EXHIBIT 2

EXPERT REPORT OF MARY DIGIORGI, MPH, PhD

I. QUALIFICATIONS

Mary DiGiorgi is the Vice President, Medical Sciences at Pacira Biosciences. Having been at Pacira for the past five years, Dr. DiGiorgi works closely with the clinical development and medical affairs teams and leads health outcomes research, medical information / communications, and publication teams and acts as lead for the Grants Committee. Prior to joining Pacira, Dr. DiGiorgi was a Clinical Research Director and Assistant Professor in the Department of Surgery at Columbia University Medical Center, and the Associate Director and teaching faculty at the Institute of Human Nutrition where she developed a health professional program and taught and developed both courses in both medical science and clinical research methodology. Dr DiGiorgi received her degrees from Columbia University: a BA from Barnard College, an MPH in epidemiology from the Mailman School of Public Health and an MS in Human Nutrition and PhD in nutritional epidemiology from the Graduate School of Arts and Sciences. My CV is attached as Exhibit A.

II. SUMMARY OF OPINIONS

A. Liposomal bupivacaine (LB) is effective at providing long-lasting pain relief. No other local anesthetic can provide extended-duration analgesia. Bupivacaine and other plain local anesthetics can only provide long-lasting pain relief if combined with other analgesics or if given to the patient through continuous infiltration via catheter.

1. The strong majority of studies, especially those that evaluate LB directly against an alternative local anesthetic in a head-to-head study, prove that LB provides longer-lasting and more effective pain reduction than alternative local anesthetics.

2. Although some studies of LB provide mixed or inconclusive results, this is not surprising and is typical of any pain medication for three reasons. First, pain is subjective and, therefore, notoriously challenging to measure accurately. Second, patients are provided additional analgesics beyond the test drugs as needed for postsurgical pain, which masks the difference in effect between the test and comparator drug. And third, patients who are recovering well are often discharged early, before the trial period has expired, which can skew the results as data is then only collected from those remaining at the end, who tend to be differently situated due to factors often related to pain which can affect recovery time.

3. Generally, only well-funded studies have the resources to conduct high-quality studies, including collecting the data necessary to account for these additional analgesics (and to perform “imputations” for that effect) and to pay to keep patients in the hospital through the duration of the trial. Results from studies that perform these imputations and minimize patient attrition are far more informative that those that do not. With respect to

LB, industry-sponsored studies are largely the only studies that accomplished these feats because they have sufficient resources to do so, while most independent studies generally do not.

4. Meta-analyses evaluating the effectiveness of analgesics also frequently result in inconclusive results; this is also true of LB. This, too, is not surprising and is not an indication that LB is not effective. Often the studies are too different to be reliably combined and the data is too limited to reach definitive conclusions. For example, because studies evaluating postsurgical analgesia must be conducted among patients undergoing similar surgeries and receiving similar analgesics, the number of test subjects is naturally limited. It is also difficult to conduct a high-quality, randomized controlled trial ("RCT"). The quality of a meta-analysis is only as good as the studies included. Therefore a meta-analysis that includes low-quality studies, and which ignores the clinical context in which they were conducted, will inevitably yield inconclusive results. In other words, "garbage in, garbage out."

B. The Hussain et al. meta-analysis suffers from a bevy of methodological and compositional errors that render it materially false. Among other concerns, the nine underlying trials are all significantly different and do not lend themselves to comparison, nor do the authors recognize that for certain procedures, the research is clear that LB provides a material benefit over alternatives. The meta-analysis is also marred by substantial selection bias. The authors exclude multiple studies that fall within their eligibility criteria and are favorable to LB, and then they include two that do not meet their eligibility criteria. One of the studies cannot even be located through a public records search, which suggests that the authors went to great lengths to locate trials that were unfavorable to LB. Of those the authors did include, several of the trials focused on LB procedures that are unapproved and/or uncommon (and therefore not yet optimized). In the end, even with these flaws, the results only, at worst, demonstrate that the benefit of LB over alternatives is inconclusive, not that is "not superior" to those alternatives.

C. The Ilfeld et al. narrative review is also deeply flawed. It likewise groups and evaluates trials involving vastly different surgical procedures. It then provides superficial reasons to dismiss much of the research that is favorable to LB. For example, the authors state that industry-sponsored studies are inherently biased, when the Cochrane Collaboration—the primary authority in the field on this subject, whose framework the authors purport to follow—does not consider industry sponsorship inherently biasing. The Cochrane Collaboration recognizes that some of the most informative studies are industry-funded. While the authors are quick to dismiss trials that are favorable to LB, they ignore—or worse, cover up—the shortcomings of a number of trials that are unfavorable to LB on which they rely.

D. The McCann Editorial compounds these errors, doubling down on Hussain's and Ilfeld's faulty methodologies and wrongly rejecting studies that demonstrate

liposomal bupivacaine's superiority based on her ill-founded animus toward industry-funded studies. She then concludes that LB's success in the market is a function of "aggressive" marketing by Pacira. However, that many of Pacira's patrons are repeat customers—primarily licensed physicians—is a testament to the drug's effectiveness, and that they continue to use LB in novel ways, beyond the common or approved uses for which Pacira sells LB, cannot be a function of Pacira's marketing.

III. OVERVIEW OF LIPOSOMAL BUPIVACAINE

Liposomal bupivacaine (LB) is the longest-acting local analgesic available, which acts directly on nerves near where it is administered to block pain signals and typically produces a numbing sensation at the skin level. In the context of surgery, it is injected near the site of surgery or directly around nerves that provide sensation to the surgical area, thereby removing or reducing pain in the area.

Bupivacaine, the active ingredient in LB, is a local anesthetic that has been used for infiltration/field block and peripheral nerve block for decades around the world. LB is bupivacaine encapsulated in microscopic spherical multivesicular liposomes (DepoFoam®), a drug delivery system consisting of a honeycomb-like structure of lipid chambers, which gradually release bupivacaine over time at the site of administration as the lipid walls begin to erode. Liposomes are among the most successful drug delivery systems used for a variety of clinical uses, designed to enhance therapeutic efficacy and reduce toxicity of conventional medicines.[1] Bupivacaine by itself (i.e., not in the liposomal capsules) provides pain relief for up to eight hours,[2] and up to 12 hours when combined with epinephrine.[3] By utilizing a liposomal delivery system, LB has been shown to provide pain relief up to 72 hours.[4]

The FDA approved LB in October 2011 for local infiltration at the surgical site to produce postsurgical analgesia in adults. In December 2015, a communication from the U.S. Food and Drug Administration (FDA) reaffirmed the broad indication for local infiltration of LB, and confirmed that the indication also includes targeted tissue plane blocks (a variation of a local infiltration), e.g., transversus abdominis plane [TAP] block), in addition to traditional direct infiltration around the surgical site. In March 2021, this indication was extended to pediatrics for use in children age six and older. In April 2018, LB was approved for administration as an interscalene brachial plexus nerve block. In November 2020, the European Commission approved LB for use in local infiltration, field blocks, as well as brachial plexus block and femoral nerve block for treatment of postsurgical pain in adults. Since its approval, LB use has been growing exponentially, with an estimated 8 million patient exposures in the United States.[5]

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[1] Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use: An updated review. Pharmaceutics. 2017; 9(2).
[2] Baxter bupivacaine HCl monograph, https://www.baxter.ca/sites/g/files/ebysai1431/files/2019-06/Bupivacaine_Hydrochloride_Injection_USP_EN.pdf.
[3] Bupivacaine HCl 0.5% with epinephrine monograph, https://pdf.hres.ca/dpd_pm/00016123.PDF.
[4] EXPAREL prescribing information 2018 https://www.pacira.com/sites/default/files/inline-files/EXPAREL_PI_Nerve_Block_Final_4-6-2018.pdf.
[5] Data on File. 6450. Parsippany, NJ: Pacira BioSciences, Inc.; January 2021.

Although LB can be used to manage postsurgical pain for a variety of surgical procedures, how effective it is over other pain relief medication is dependent on the procedure and the technique used by the anesthesiologist. LB is most valuable when used for procedures in which moderate to severe postsurgical pain is expected to last beyond 24 hours or require larger doses of opioids, or in patients at higher risk for opioid-related adverse drug events. LB is also more effective when all clinical team members are educated about infiltration technique and its appropriate use as part of a multimodal approach to manage postsurgical pain.

Where moderate to severe pain is not expected to last beyond 24 hours, immediate release local anesthetics may be sufficient. However, when surgeries are likely to require treatment for pain for longer periods, a single dose of an immediate-release local anesthetic and other drugs used to help, such as opioids and anti-inflammatories, have limited duration and may have potential side effects.[6,7] Continuous catheter infusion of those anesthetics have been shown to provide prolonged pain control, but it is time- and resource-intensive, delivers high total doses of local anesthetics, is associated with risk of complications such as device failure and infection, and is subject to user error.[8,9] In contrast, a single administration of LB can provide prolonged pain control greater than 24 hours, while decreasing costs and the risk of complications that come with continuous infusion.

IV. LIPOSOMAL BUPIVACAINE PROVIDES A SAFE, EFFECTIVE, AND OPIOID-FREE ANALGESIC OPTION.

LB is an effective method for prolonged postoperative pain management. It is the longest-acting local anesthetic that FDA has approved, and in so doing, the FDA noted that its efficacy lasts for days rather than hours. LB is also recommended by multiple professional societies, and the balance of studies about LB recognize the benefits it can offer over other forms of anesthetics and pain treatments used for extended postoperative treatment (i.e., pain expected to last more than 24 hours).

Notably, nearly ten years ago, in October 2011 the FDA approved the use of liposomal bupivacaine. The FDA relied on data from three Phase III studies in approving LB. Two of the three were RCTs that were published in peer-review journals.[10, 11] Comparing LB to a placebo, the studies found pain scores improved, as well as postsurgical opioid use, time until first opioid

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[6] Pearson AME, Kaushal A, Crawford MW et al. Dexamethasone as an adjuvant to peripheral nerve block. Cochrane Database Syst. Rev. 2017 Nov; 2017(11).
[7] Albrecht E, Kern C, Kirkham KR. A systematic review and meta-analysis of perineural dexamethasone for peripheral nerve blocks. Anaesthesia. 2015 Jan; 70(1):71-83.
[8] Joshi G, Gandhi K, Shah N, Gadsden J, Corman SL. Peripheral nerve blocks in the management of postoperative pain: challenges and opportunities. *J Clin Anesth* 2016; 35: 502 524-29.
[9] Capdevila X, Pirat P, Bringuier S, et al. Continuous peripheral nerve blocks in hospital wards after orthopedic surgery: a multicenter prospective analysis of the quality of postoperative analgesia and complications in 1,416 patients. *Anesthesiology.* 2005 Nov; 103(5):1035-45.
[10] Golf M, Daniels SE, Onel E. A phase 3, randomized, placebo-controlled trial of DepoFoam® bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. Advances in therapy. 2011; 28(9):776-88.
[11] Gorfine SR, Onel E, Patou G, Krivokapic ZV. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. Diseases of the colon and rectum. 2011; 54(12):1552-9.

use, and patient satisfaction.[12] These were multicenter, randomized, double-blind, placebo-controlled studies. The FDA then expanded approval of LB in 2018 to include interscalene brachial plexus nerve blocks,[13] and recently, in March 2021, expanded the approved use in local infiltration to include pediatrics based on additional RCTs.[14] Similarly, in 2018, the Centers for Medicare and Medicaid Services (CMS) reviewed studies of LB and other non-opioid pain treatments and, based on those studies, determined that it would pay separately for use of LB (sold as EXPAREL®) at ambulatory surgical centers, rather than as part of the bundled payment process, but not for any other non-opioid pain medication. CMS concluded that, unlike for LB, it "ha[s] not found compelling evidence for other non-opioid pain management drugs described above to warrant separate payment at this time."[15]

Professional societies across multiple medical practice areas also recognize the benefit of LB and either recommend its use or recommend that its healthcare provider members be familiar with what LB can provide patients. These include, among others, the following recommendations in Table 1:

Table 1. Liposomal Bupivacaine in Professional Society Guidelines

Practice Area	Year	Society	Recommendation
Anesthesiology	2016	American Pain Society (APS), American Society of Regional Anesthesia and Pain Medicine (ASRA), and American Society of Anesthesiologists (ASA)	Recommendation for site-specific local anesthetic infiltration for surgical procedures, noting that "clinicians should be knowledgeable regarding specific local anesthetic infiltration techniques, including the use of extended-release formulations of local anesthetics such as liposomal bupivacaine."[16]
Colorectal Surgery	2016	American Society of Colon and Rectal Surgeons (ASCRS), Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Strong recommendation for the use of a perioperative multimodal, opioid-sparing, pain management plan, noting that liposomal bupivacaine wound infiltration and transversus abdominis plane (TAP) blocks "have shown promising results in

[12] Food and Drug Administration (FDA). Guidance for Industry Analgesic Indications: Developing Drug and Biological Products. February 2014. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm384691.pdf

[13] Patel MA, Gadsden JC, Nedeljkovic SS, Bao X, Zeballos JL, Yu V, et al. Brachial Plexus Block with Liposomal Bupivacaine for Shoulder Surgery Improves Analgesia and Reduces Opioid Consumption: Results from a Multicenter, Randomized, Double-Blind, Controlled Trial. Pain Med. 2020; 21(2):387-400.

[14] Tirotta C, Jose de Armendi A, Horn ND, Hammer GB, Szczodry M, Matuszczak ME, et al. Play: A Phase 3 Study Of Pharmacokinetics And Safety Of Liposomal Bupivacaine For Pediatric Surgery. ASA - American Society of Anesthesiologists Annual Meeting; Washington, D.C. 2020.

[15] Federal Register, Vol. 83, No. 225 at 59069 (Nov. 1, 2018).

[16] Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. The journal of pain: official journal of the American Pain Society. 2016; 17(2):131-57.

			patients undergoing open and laparoscopic colorectal surgery."[17]
Breast Reconstruction	2017	ERAS Society	Strong recommendation for the use of multimodal opioid-sparing postoperative pain management regimens, noting that "[a] single injection of liposomal bupivacaine lasts for several days, potentially avoiding the need for catheter-based infusions."[18]
Colorectal Surgery	2018	ERAS Society	Strong recommendation for the use of TAP blocks for minimally invasive colorectal surgery, noting that shorter acting local anesthetics have limited duration. Liposomal bupivacaine is included as an alternative to extend the duration.[19]
Gynecologic Oncology	2019	ERAS Society	Strong recommendation for a multimodal post-operative analgesic protocol using non-opioid oral medications and incisional injection of local anesthetic to decrease the need for systemic medications, stating that "[i]ncisional infiltration with either bupivacaine or liposomal bupivacaine has no systemic side effects when used appropriately, and should be incorporated into all ERAS protocols as a component of multimodal analgesia."[20]
Thoracic Surgery	2018	ERAS Society, European Society of Thoracic Surgeons (ESTS)	Recommendation for peripheral nerve blocks over thoracic epidural, noting that "liposomal bupivacaine also shows promise when delivered as multilevel intercostal injections, potentially providing blockade of intercostal nerves for up to 96 hours."[21]
Vulvar and Vaginal Surgery	2020	ERAS Society	Recommendation for a multimodal postoperative analgesic protocol with minimal opioids prescribed at discharge, noting that "there is some support for using local anesthetics, especially for paracervical and vaginal cuff blocks; liposomal bupivacaine may be helpful but still requires further study."[22]

[17] Carmichael JC, Keller DS, Baldini G, Bordeianou L, Weiss E, Lee L, et al. Clinical Practice Guidelines for Enhanced Recovery After Colon and Rectal Surgery From the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons. Dis Colon Rectum. 2017; 60(8):761-84.
[18] Temple-Oberle C, Shea-Budgell MA, Tan M, Semple JL, Schrag C, Barreto M, et al. Consensus Review of Optimal Perioperative Care in Breast Reconstruction: Enhanced Recovery after Surgery (ERAS) Society Recommendations. Plast Reconstr Surg. 2017; 139(5):1056e-71e.
[19] Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations: 2018. World J Surg. 2019 Mar; 43(3):659-695.
[20] Nelson G, Bakkum-Gamez J, Kalogera E, Glaser G, Altman A, Meyer LA, et al. Guidelines for perioperative care in gynecologic/oncology: Enhanced Recovery After Surgery (ERAS) Society recommendations-2019 update. Int J Gynecol Cancer. 2019 Mar 15. [Epub ahead of print]
[21] Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, Brunelli A, Cerfolio RJ, Gonzalez M, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS(R)) Society and the European Society of Thoracic Surgeons (ESTS). European journal of cardio-thoracic surgery: official journal of the European Association for Cardio-thoracic Surgery. 2019; 55(1):91-115.
[22] Alon D. Altman, Magali Robert, Robert Armbrust, William J. Fawcett, Mikio Nihira, Chris N. Jones, Karl Tamussino, Jalid Sehouli, Sean C. Dowdy, Gregg Nelson, Guidelines for vulvar and vaginal surgery: Enhanced Recovery After Surgery Society recommendations, American Journal of Obstetrics and Gynecology, 2020; 223(4): 475-485.

LB has been studied at length, and the balance of these studies demonstrates LB is an effective form of analgesia with benefits over non-liposomal bupivacaine. Indeed, the Hussain review itself recognizes that pharmacokinetic studies corroborate LB's effective slow release of bupivacaine, "showing sustained plasma bupivacaine levels up to 96 h[ours] and even 120 h[ours] after interscalene brachial plexus block."[23] Further, there is a reason the FDA approved use of LB in October 2011. Based on two successful trials in nociceptive pain (meaning two studies in which patients had a reduced perception or sensation of pain), FDA approved LB for administration into a surgical site as a wound infiltration/field block analgesia across all surgical sites.[24] These were multicenter, randomized, double-blind, placebo-controlled studies. The FDA also expanded approval of LB in 2018 to include interscalene brachial plexus nerve blocks based on an additional multicenter, randomized, double-blind, placebo-controlled study.

Since approval, clinical and economic outcomes associated with LB use have been evaluated, reviewed, and discussed in hundreds of journal articles, conference presentations, and abstracts across many surgical areas and within a wide variety of analgesic protocols. LB has received substantial attention, especially as efforts have evolved in recent years to focus on improving pain management and reducing opioid use after surgery. Early studies often compared LB to opioids and demonstrated that LB provides superior pain control and significantly reduces the need for opioids. For example, the Yalmachnili RCT, presented in 2015, examined 100 patients who underwent laparotomy, a major abdominal procedure, compared patients receiving (1) LB, (2) intravascular opioids alone, and (3) a continuous infusion of bupivacaine. Patients who received LB showed a 52% reduction in total opioid consumption compared to the patients who received opioids only (101.3 versus 210.2 mg morphine equivalents through postoperative day 3; $p<0.001$), and a 43% reduction compared to patients who received continuous bupivacaine infusion (101.3 versus 177.8 mg morphine equivalents through postoperative day 3; $p<0.001$), as well as lower pain scores through postoperative day 3 ($p \leq 0.005$), and fewer opioid-related side effects compared to both groups ($p = 0.002$).[25] Over time, studies have evolved and now often evaluate LB as part of a regimen of multiple types of non-opioid treatments (in technical terms, opioid-sparing multimodal analgesic protocols). In total, over 150 primary research studies have been published to date which evaluate the use of LB compared to an alternate regional anesthesia in real-world uses. Studies have been conducted as either RCTs, or as observational studies that were part of a continuous quality improvement evaluation to provide evidence of improved patient care.

In order to provide an overview of the available LB research, I conducted a systematic literature search and reviewed all primary clinical research manuscripts that I found that were published in peer-reviewed journals between January 1, 2011, and February 28, 2021, and which

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[23] Hussain N, Brull R, Sheehy B, Essandoh MK, Stahl DL, Weaver TE, et al. Perineural Liposomal Bupivacaine Is Not Superior to Nonliposomal Bupivacaine for Peripheral Nerve Block Analgesia. Anesthesiology. 2021; 134: 147-64, at 11. (Hereinafter "Hussain.")

[24] Food and Drug Administration (FDA). Guidance for Industry Analgesic Indications: Developing Drug and Biological Products. February 2014. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm384691.pdf.

[25] Yalmanchili HM, Buchanan SN, Chambers LW, et al. Postlaparotomy pain management: Comparison of patient-controlled analgesia pump alone, with subcutaneous bupivacaine infusion, or with injection of liposomal bupivacaine suspension. *J Opioid Manag.* 2019; 15(2):169-175.

evaluated the effectiveness of LB versus immediate-release local anesthetics (i.e., "head-to-head" studies) across a broad range of procedures. Together, these evaluate various outcomes, including pain reduction, opioid reduction, improved function, shortened hospital stay, safety, and/or procedural convenience/cost. (See Appendix I, methods of study selection). The head-to-head studies were conducted primarily to assess the use of LB in a variety of real-world practice settings and are overwhelmingly favorable toward LB. These studies provide more information on clinical context and further confirm the wide applicability across appropriate surgical procedures and the need to provide clinicians with additional non-opioid options to manage pain.

Table 2. Published head-to-head studies

Favorability is defined as author's conclusions of findings including pain, opioid use, function, hospital stay, cost and/or safety. (Citations available in Appendix II.)

Procedural Area	Total N	No. Studies	Design (RCT | Obs)	% Favorable
Orthopedic	19,320	95	40 | 55	56%
OB/GYN	1,142	12	9 | 3	67%
Plastic	1,040	13	7 | 6	69%
General	1,074	6	4 | 2	67%
Cardiothoracic	6,261	21	2 | 19	67%
Colorectal	1,866	7	4 | 3	86%
Urologic	641	7	4 | 3	29%
Pediatric	326	3	0 | 3	100%
Other*	1,056	8	3 | 5	62%

*Procedural areas: dental (3), ophthalmology (1), transplant (2), trauma (1), multiple (1)

Although the results can vary by procedural area, when LB is evaluated directly against an immediate-release local anesthetic, the strong majority of studies are favorable to LB, and therefore demonstrate its effectiveness overall.

Many of these studies also specifically demonstrate that LB is superior to non-liposomal bupivacaine, at least for specific procedural areas. For example, the multi-center PILLAR trial randomized 139 subjects undergoing total knee replacements into two groups: an experimental group receiving non-liposomal bupivacaine and LB, and a control group receiving only non-liposomal bupivacaine. Investigators followed a standardized infiltration technique, which is important to providing complete coverage of the surgical site. The results were overwhelmingly positive. The experimental group had much-improved pain scores and the average opioid consumption in the first 48 hours was only 16 mg for experimental group compared to 80 mg for the control group.[26]

In another study, an RCT of patients undergoing surgery to address a condition in their hands called Dupuytren contractures were randomized into an experimental group receiving a mixture of bupivacaine and LB and a control group receiving bupivacaine alone. The

[26] Mont MA, Beaver WB, Dysart SH, Barrington JW, Del Gaizo DJ: Corrigendum to "local infiltration analgesia with liposomal bupivacaine improves pain scores and reduces opioid use after total knee arthroplasty: Results of a randomized controlled trial" [Journal of Arthroplasty 33 (2018) 90-96]. J Arthroplasty 2019; 34:399-400.

experimental group had average pain score improvements of between 1 to 2 points (on an 11-point scale).[27] And an RCT of 40 patients undergoing bunion repair surgery were randomized into three groups, one receiving only general anesthesia, one receiving LB and bupivacaine, and a third receiving bupivacaine alone. The group receiving the bupivacaine and LB combination required much lower doses of opioids—only 9.6 mg of morphine equivalents, compared to 26.8 mg in the bupivacaine-alone group and 60.4 mg in the general anesthesia group.[28]

Similarly, the Mayo Clinic in Rochester, Minnesota, was an early adopter of enhanced recovery protocols, which included a multimodal analgesic regimen. They conducted a large study of 358 patients to compare local infiltration of LB to bupivacaine as part of an opioid-minimized enhanced recovery protocol for patients undergoing similar procedures. Their study showed that LB was able to provide comparable pain scores to plain bupivacaine plus other analgesics while requiring fewer opioids and having fewer opioid-related side effects.[29] This study has been cited in guidelines which recommend the use of LB[30] as well as a call to action for implementing enhanced recovery protocols for cesarean sections.[31]

To be sure, as is observed with other local anesthetics, studies are not uniformly positive for LB. The studies make clear that the efficacy of LB depends on the specific surgical procedure, use of LB (i.e., direct infiltration/tissue plane block or peripheral nerve block), and proper execution by the anesthesiologist. For example, as discussed more below, studies strongly favor LB for certain uses in colorectal surgeries and gynecological oncology surgeries. But the benefits that LB can provide compared to other alternatives are more mixed with respect to, e.g., urologic procedures, such as urethral sling procedures, which are associated with prolonged pain that may be experienced beyond the surgical area. The medical field also continues to learn how to best use LB for specific surgical procedures, in terms of e.g., proper dose. In general, regional anesthesia is a rapidly evolving field which continues to develop new approaches for improved pain management. I anticipate that in time, LB will prove to be effective for more surgical procedures than currently demonstrated as physicians and researchers continue to evolve best practice for regional anesthesia and the use of LB.

Although LB studies are not universally favorable, this is not surprising. Studies of pain treatments—not just LB—often result in mixed outcomes. In discussing the challenge of developing analgesics, Sharon Hertz, MD, Director of the FDA Division of Anesthesia, Analgesia and Addiction Products noted that clinical trials of analgesics are "unpredictable," stating that "[a] number of pharmacologic treatments examined in recent randomized clinical

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[27] Vandepitte C, et al.: Effect of Bupivacaine Liposome Injectable Suspension on Sensory Blockade and Analgesia for Dupuytren Contracture Release. J. of Hand Surgery Global Online 2019; 191-197.

[28] Van Boxstael S, et al.: Analgesia after Hallux Valgus Osteotomy Posterior Tibial and Deep Peroneal Nerve Ankle Blocks with Bupivacaine Liposome Injectable Suspension+Bupivacaine HCl vs. Bupivacaine HCl vs. General Anesthesia Alone: A Randomized Clinical Trial. Clinical Res Foot Ankle 2019, 7:3.

[29] Kalogera E, Bakkum-Gamez JN, Weaver AL, Moriarty JP, Borah BJ, Langstraat CL, et al. Abdominal Incision Injection of Liposomal Bupivacaine and Opioid Use After Laparotomy for Gynecologic Malignancies. Obstet Gynecol. 2016; 128(5):1009-17.

[30] Nelson G, Bakkum-Gamez J, Kalogera E, Glaser G, Altman A, Meyer LA, et al. Guidelines for perioperative care in gynecologic/oncology: Enhanced Recovery After Surgery (ERAS) Society recommendations-2019 update. Int J Gynecol Cancer. 2019 Mar 15.

[31] Peahl AF, Smith R, Johnson T, Morgan D, Pearlman M. Better late than never: why obstetricians must implement enhanced recovery after cesarean. American Journal of Obstetrics & Gynecology. 2019.

trials have failed to show statistically significant superiority to placebo in conditions in which their efficacy had previously been demonstrated."[32] Pain trials often fail due to complexities of measuring pain and the need for concomitant analgesics.[33,34,35] In addition, comparative studies can show a lack of difference in pain scores due to many factors, primarily the subjectivity of pain and prescribing practices in which over-prescribing opioids negates any ability to detect a difference in pain outcomes.

Said another way, pain trials (including trials of LB) often show no difference between treatments when, in fact, there is a difference. First, pain is subjective and difficult to measure accurately. What one patient self-identifies as a "level 3" pain, another patient may identify as a "level 6." Additionally—and this is a significant problem—patients in trials receive other analgesics beyond the test drugs. Ethically, patients cannot be left in pain. If they are in pain, they receive "rescue" medication as needed to control it. As a result, it can be exceedingly difficult to tease out the impact of a single drug when multiple drugs are needed to manage pain. Often these studies do not take into account these challenges and are often significantly underpowered to detect differences between treatment groups. Indeed, the fact that such a large majority of head-to-head LB studies *are* favorable is, itself, striking. For this reason, the ASA itself has issued guidelines that recommend various anesthetic treatments, even when the studies are inconclusive or mixed.[36]

At bottom, it is *simply impossible* for LB to be no different than plain bupivacaine or similar other local anesthetics. This is an important point to understand. Until LB, a single dose of a plain local anesthetic by itself has been shown to provide pain relief only up to ten hours.[37] The *only way* other local anesthetics can provide pain relief much beyond 10 hours is if they are combined with other medications, such as epinephrine,[38] which gives a few additional hours of relief, or provided through more than one dose, such as a continuous infiltration through a catheter. But as noted earlier, catheter infusions are not ideal.

Thus, the balance of research on liposomal bupivacaine demonstrates that it provides prolonged pain relief and is superior to other local anesthetics, including non-liposomal bupivacaine. The approval by the FDA and endorsement by various professional societies

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[32] Hertz S. Challenge of Developing New Pain Medicines – Developing Novel Analgesics and Abuse-Deterrent Opioid Formulations. FDA Science Board, March 1, 2016.
[33] *Id.*
[34] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry. November 2016.
[35] Cui Y et al. Intra-articular bupivacaine after joint arthroplasty: a systematic review and meta-analysis of randomized placebo-controlled studies BMJ Open 2016; 6:e011325 [many bupivacaine trials also have failed].
[36] ASA, "Practice Guidelines for Acute Pain Management in the Perioperative Setting" at 253 (recommending "peripheral regional techniques" even though the evidence was largely equivocal or the number of studies was insufficient) [hereinafter "ASA Practice Guidelines"], available at https://www.asahq.org/~/media/sites/asahq/files/public/resources/standards-guidelines/practice-guidelines-for-acute-pain-management-in-the-perioperative-setting.pdf.
[37] Ropivacaine prescribing information https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020533s035lbl.pdf; Baxter bupivacaine HCl monograph, https://www.baxter.ca/sites/g/files/ebysai1431/files/2019-06/Bupivacaine_Hydrochloride_Injection_USP_EN.pdf.
[38] Bupivacaine HCl 0.5% with epinephrine monograph, https://pdf.hres.ca/dpd_pm/00016123.PDF.

reaffirms this conclusion. It is not surprising that not all studies uniformly demonstrate a benefit of LB due to the complexities of any pain treatment trial and the fact that LB's value depends on the precise technique used, proper implementation, and the specific surgical area involved.

V. THE FEBRUARY 2021 EDITION OF *ANESTHESIOLOGY* PUBLISHED THREE ARTICLES CONTAINING FALSE CONCLUSIONS ABOUT LIPOSOMAL BUPIVACAINE.

The February 2021 issue of *Anesthesiology* contained three articles that were critical of LB. Each of these contains false conclusions about the effectiveness of LB.

A. The Hussain "Meta-Analysis" Contains False Conclusions—It Reviewed an Overly Circumscribed Universe of Studies and Failed to Recognize Differences in Results Among Surgical Procedures.

The first article, by Dr. Nasir Hussain et al., identifies itself as a "systematic review and meta-analysis."[39] A systematic review is a review of the scientific evidence of a pre-specified question using thorough and specific methodology to identify, select and critically appraise relevant primary research. A meta-analysis, which combines the studies and analyzes them to assess specific outcomes, can then be conducted if the studies located in the systematic review are sufficiently similar in their methodologies and outcome assessments.[40]

The authors claim to have searched for and reviewed "randomized trials that compared the effect of perineural liposomal bupivacaine with nonliposomal local anesthetics[.]"[41] Upon review of those trials, the authors conclude—as stated prominently in the title—that LB "is not superior" to non-liposomal bupivacaine for nerve block analgesia. However, this bold statement is false.

First, the authors' blanket conclusion masks the differences of LB's benefit by procedural area and type of use of LB. Although current research may not yet demonstrate as much benefit of LB for certain uses, such as dorsal penile nerve block and penile ring block for inflatable penile prosthesis (IPP) placement—which one of the studies analyzed by Hussain et al. examined—the evidence is strong with respect to other uses. For example, research strongly supports the use of LB with respect to interscalene brachial plexus block (a peripheral nerve block) for rotator cuff repair or shoulder arthroplasty. The authors' all-inclusive statement that LB is flatly "not superior" to non-liposomal bupivacaine is false because for certain treatments it is demonstrably superior, particularly with adequate dosing and proper technique.

Second, the authors carefully curate the trials for review, allowing them to reach what appears to be a pre-determined outcome. I am aware of at least four studies that satisfy the

[39] Hussain at 1.
[40] Undertaking Systematic Reviews of Research on Effectiveness. CRD's Guidance for those Carrying Out or Commissioning Reviews. CRD Report Number 4 (2nd Edition). NHS Centre for Reviews and Dissemination, University of York. March 2001.
[41] Hussain at 2.

authors' eligibility criteria—all of which were favorable to LB—but which the authors did not include:

- Sethi PM, Brameier DT, Mandava NK, Miller SR. Liposomal bupivacaine reduces opiate consumption after rotator cuff repair in a randomized controlled trial. J Shoulder Elbow Surg. 2019 May; 28(5):819-827;

- Belsh Y, et al. A Prospective, Randomized, Double-Blind, Controlled Trial Comparing Liposomal Bupivacaine with Ropivacaine in Adductor Canal Block for Total Knee Arthroplasty Patients. 2018 World Congress on Regional Anesthesia & Pain Med. April 19-21, 2018;[42]

- Vandepitte C, et al.: Effect of Bupivacaine Liposome Injectable Suspension on Sensory Blockade and Analgesia for Dupuytren Contracture Release. J. of Hand Surgery Global Online 2019; 191-197; and

- Van Boxstael S, et al.: Analgesia after Hallux Valgus Osteotomy Posterior Tibial and Deep Peroneal Nerve Ankle Blocks with Bupivacaine Liposome Injectable Suspension+Bupivacaine HCl vs. Bupivacaine HCl vs. General Anesthesia Alone: A Randomized Clinical Trial. Clinical Res Foot Ankle 2019, 7:3.

Additionally, the Hussain analysis authors included a trial by Vandepitte that was favorable to LB. However, the authors recommended that the trial results be disregarded simply because the trial was industry-funded. This strategic decision fundamentally changed the results of the meta-analysis from one in which the results showed a *statistically significant* improvement in pain when LB was used over a local anesthetic, to a benefit the authors deemed clinically "nonsignificant."[43] Medical publishing standards do not countenance discounting industry-funded studies on that basis alone. The Cochrane Risk of Bias tool, a standard tool used to assess risk in systematic reviews and meta-analyses,[44] does not include industry funding in their assessment tool.[45] It acknowledges that any bias that may be introduced is, at most, uncertain. The Cochrane handbook states: "financial conflicts of interest are less important in a trial initiated, designed, analysed and reported by academics adhering to the arm's length principle when acquiring free trial medication from a drug company, and where lead authors have no conflicts of interest."[46] This describes the conditions of the Vandepitte trial, which was funded as

[42] This study compared LB to ropivacaine, which is highly similar to bupivacaine, and would fall within the Hussain eligibility criteria of "nonliposomal local anesthetics." Although the Belsh study is only an abstract without full text, it contains the relevant data. Several of the trials included in the Hussain analysis were also unpublished and did not contain full texts: Badman (published after the Hussain analysis was prepared), Shariat, Cios, and Khandhar.
[43] Hussain at 1.
[44] The Cochrane Collaboration is an independent nonprofit organization whose "main purpose..is to develop systematic reviews of the strongest evidence available about healthcare interventions." [About the Cochrane Collaboration. Available at https://consumers.cochrane.org/about-cochrane-collaboration.]
[45] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366:l4898. Available from https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool?authuser=0.
[46] Boutron I, Page MJ, Higgins JPT, Altman DG, Lundh A, Hróbjartsson A. Chapter 7, Section 8.6: Considering bias and conflicts of interest among the included studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T,

an investigator-initiated grant. Indeed, the authors of the Hussain paper themselves recognize that the Vandepitte trial was *the most sound of any of the underlying studies.* Figure 2 on page 7 of the Hussain analysis analyzes each of the studies for common markers for bias and low quality data. Vandepitte was the only study not to demonstrate indicia of bias.

The authors also *included* two studies they should have excluded. One of the nine trials was by Zhang et al. The Zhang study relates to a pec block, a type of a tissue plane block[47]—not a peripheral nerve block—the subject of the Hussain analysis. The Hussain analysis claims to have excluded tissue plane block studies. I also searched extensively for the Zhang and could not locate it. Among other locations, I searched Google Scholar, PubMed and Embase, and clinicaltrials.gov. Pacira finally obtained a copy only through a request to the authors of the Hussain analysis. The fact that I could not locate it suggests that the authors went to some effort to find studies that were not favorable to LB. Further, Additionally, the Hussain paper includes a Xie trial, but that trial does not report data in an extractable form.

It is precisely this selection bias that the Cochrane Collaboration Handbook warns can occur in meta-analyses and which can skew the results: "The first is in the results of the individual studies included in a systematic review. Since the conclusions drawn in a review depend on the results of the included studies, if these results are biased, then a meta-analysis of the studies will produce a misleading conclusion."[48]

Third, the Hussain analysis relied on studies with considerable clinical and methodological differences that are not susceptible to comparison. The underlying trials of LB involved vastly different surgical procedures, different types of nerve blocks, and different volume and doses of LB. The nine underlying studies covered nine different surgeries: "major shoulder surgery, rotator cuff surgery, arthroscopic shoulder surgery, hip arthroscopy, total knee arthroplasty, video-assisted thoracoscopic surgery, minimally invasive lung resection, inflatable penile prosthesis placement, and total mastectomy."[49] The studies also covered six different types of nerve blocks: "interscalene nerve block, adductor canal block, intercostal nerve block, dorsal penile block, fascia iliaca block, and pectoralis myofascial plane block."[50] Further, the volume and dose of LB ranged from 10 to 40 ml of LB and 88 to 266 mg. In other words, the authors chose studies that were inappropriate to group together to evaluate a common outcome.[51]

Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

[47] Blanco R, Barrington MJ. Pectoralis and Serratus Plane Nerve Blocks. NYSORA. Available from https://www.nysora.com/regional-anesthesia-for-specific-surgical-procedures/thorax/pectoralis-serratus-plane-blocks/.

[48] Boutron I, Page MJ, Higgins JPT, Altman DG, Lundh A, Hróbjartsson A. Chapter 7: Considering bias and conflicts of interest among the included studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

[49] Hussain at 4.

[50] *Id.*

[51] In addition to these methodological differences, the studies are also characterized by statistical heterogeneity, despite the authors' repeated claims to the contrary. For the primary outcome, scores for "area under the curve" (which are an assessment of reported pain levels), the authors state that the studies had low heterogeneity, but they fail to report to the I^2 statistic to confirm. For the secondary outcome of reduced opioid consumption, the authors define severe heterogeneity as an I^2 calculation of 50% or greater, rather than the standard 40%. Even by their own standard, however, the I^2 calculation was 68% for the 25-48 hour pain results, and narrowly carves out results for the

ASA's own practice demonstrates that this is not an acceptable method. In ASA's 2012 "Practice Guidelines for Acute Pain Management in the Perioperative Setting," they separately assess randomized controlled trials not only by body area *but also by timing of administration* (i.e., whether the drug was provided pre- or post-surgical incision).[52]

Fifth, not only did the authors review trials about very different types of procedures, many of those procedures did not relate to the most effective uses of LB—as noted above, the success of LB varies by procedure and specific technique. For example, the studies included a penile block for prosthesis placement and a fascia iliaca block for hip arthroscopy, which are not common uses of LB and for which research has not yet identified if there is an optimal dose and technique for which LB, as well as other local anesthetics, would be particularly effective. The trials did include three that looked at LB as an interscalene blocking agent in shoulder surgeries, which is a common use of LB, but one of those studies (Shariat [reference 76]) was conducted prior to FDA approval and before Pacira had determined the optimal dose of LB for that use (133 mg); accordingly, the study used only 88 mg as the dosage. It was conducted as a pilot study, meaning that data for using LB in this manner did not exist yet, and the purpose of the study was to experiment with different doses and techniques to assess whether this might be a viable treatment and at what dose. The other two interscalene trials (Badman [reference 73] and Vandepitte [reference 71]) both used 133 mg and reached favorable outcomes for LB. Indeed, because the Vandepitte study was published while Pacira was conducting its Phase 3 interscalene trial, Pacira used it to inform the optimal dosing for the Phase 3 trial.

Sixth, the authors' own analysis does not support the conclusion stated in the title. Rather, at most, the review supports a conclusion only that it is inconclusive whether LB is superior to non-liposomal bupivacaine. Indeed, that is what the editor comments at the top state, that "*it remains unclear*."[53] And the authors' conclusion that LB is "not superior" to non-liposomal bupivacaine is counter to their own acknowledgment that the results demonstrate a "statistically significant" difference between LB and non-liposomal bupivacaine. Reaching an opinion any stronger than "inconclusive" would be to extrapolate from the underlying studies beyond the bounds of what they reasonably permit for two reasons: (1) the diversity of the underlying studies (discussed above), and (2) the poor quality of the data. According to the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework utilized by the Hussain study, studies have low-quality data when, for example, they are small, not randomized, have known or unknown risks of bias, weak *P* value,- or incomplete outcome data.[54] The Hussain analysis authors reviewed underlying trials that were marked by poor-quality data, as is evidenced by their own risk of methodologic bias assessment depicted in Figure 2 (p. 7), showing shortcomings in all studies with the exception, ironically, of the study by Vandepitte, which they excluded from their final calculation due to what they deem conflict-of-interest bias.

Indeed, for these reasons (poor quality and diversity of underlying data), among others, it is not uncommon for meta-analyses and systematic reviews to reach inconclusive results. A review of LB meta-analyses and systematic reviews demonstrates the same issue with LB. My

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49-72 hour pain, which were 49% (which would have demonstrated statistical heterogeneity under the standard 48% threshold).

[52] *Supra* n.36, ASA Practice Guidelines at 253.

[53] Hussain at 1.

[54] https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/

literature review identified 35 such reviews related to LB. Sixty-five percent of these reviews (23 of 35) report some benefit of LB over the comparator. Nevertheless, 22 of 35 ultimately result in inconclusive or cautiously optimistic findings due to the high degree of heterogeneity across studies and/or a lack of high-quality data, which is typical of pain studies in general. Table 3 provides various examples of these types of conclusions. This stands in contrast to the head-to-head studies that had more definitive outcomes, most of which were favorable to LB.

Table 3. Inconclusive or Neutral Meta-Analyses and Systematic Reviews Due to Limited High Quality Evidence

Year	Procedural Area	Study	LB Administration	Studies Included	Authors' Conclusions
2017	Various Surgical Procedures	Hamilton TW, et al. Cochrane Database of Systematic Reviews. 2017; 2:CD011419.	LB Local infiltration	9 RCTs in systematic review, none in meta-analysis	LB appears to reduce pain compared to placebo, however, the limited evidence does not demonstrate superiority to bupivacaine hydrochloride. Due to the low quality and volume of evidence our confidence in the effect estimate is limited. the true effect may be substantially different from our estimate.
2018	Colorectal Surgery	Raman S, et al. Journal of Drug Assessment. 2018; 7(1):43-50.	Colorectal Resections	7 studies (1008 patients)	LB is associated with decreased IV opioid use, length of stay and lower pain scores. However, our data needs to be interpreted cautiously given the relative paucity of randomized controlled trials.
2020	Colorectal Surgery	Byrnes KG, et al. Colorectal Dis. 2020.	Colorectal Enhanced Recovery Pathways	12 studies (2512 patients)	LB reduced opioids and hospital stay, however the confidence in these estimates was graded as very low. Further well-executed trials are needed.
2020	Plastic Surgery	Abdou SA, et al. Journal of reconstructive microsurgery. 2020;36(5):353-61.	LB TAP vs. LA single shot TAP vs. continuous TAP Microsurgical Breast Reconstruction	10 studies (684 patients) – LB: 4 studies (139 patients)	Data support the use of TAP blocks in autologous breast reconstruction, however additional large studies with more standardized protocol are needed
2019	Orthopedic Procedures	Zhao B, et al. Medicine (Baltimore). 2019; 98(3):e14092	LB local infiltration vs. LA infiltration	12 RCTs	Comparable pain control at 24h and 48h, comparable nausea and LOS, significant reduction in opioids at

Year	Procedural Area	Study	LB Administration	Studies Included	Authors' Conclusions
			Total joint arthroplasty (TKA/THA)		24h (P<.0001), and 48h (P=.0008). However, additional high quality studies needed for more conclusive evidence
2017	Shoulder Procedures	Yan Z, et al. Medicine. 2017; 96(27):e7226.	LB local infiltration LB vs. LA interscalene block Total shoulder arthroplasty	5 studies (573 patients)	LB local infiltration comparable on reducing both pain scores and the hospital stay. However, large, higher quality studies needed
2017	Total Hip Arthroplasty	Zhang X, et al. Medicine. 2017; 96(49):e8433..		4 studies (308 patients)	LB could significantly reduce pain, opioid use within the first 48 hours and nausea and vomiting. The overall evidence level was low. Further research is likely to significantly alter confidence levels in the effect, as well as potentially changing the estimate
2016	Total Knee Arthroplasty	Wu ZQ, et al. J Orthop Surg Res. 2016; 11(1):84.	LB local infiltration vs. various comparators (including continuous infiltration and nerve block)	5 studies (574 patients)	LB demonstrated better pain control; however, the sample size was limited. Further RCTs are needed
2017	Total Knee Arhroplasty	Singh PM, et al. Journal of Arthroplasty. 2017; 32(2):675-88.e1		16 studies	LB associated with shorter hospital stay and better pain control, but superiority and/or inferiority could not be established and results may not be clinically meaningful due to low quality/high heterogeneity

These results are not surprising and do not provide a sound basis to conclude that LB does not provide benefits over non-liposomal bupivacaine. When clinical studies of a drug or medical device are characterized by substantial diversity (e.g., studying different uses of the medication in different surgical sites at different dosages among different populations with different pain regimens), inconsistent findings across meta-analyses and results that conflict with large randomized controlled trials are not uncommon. Given that LB can be used in many different types of procedures and in different manners (i.e., site infiltration versus a nerve blocking agent), in which the effectiveness varies by type and use, and that study designs vary and other analgesics are typically provided, one would expect inconclusive or neutral conclusions. This likelihood is compounded by the large volume of LB studies that produced

low-quality data. Accordingly, meta-analyses and systematic reviews can create a misleading impression by diminishing the findings of effectiveness of pain treatments. Thus, interpretation of meta-analyses and systematic reviews, especially with respect to LB must be approached with caution. This is why a systematic review of all head-to-head studies, as I performed, provides a more comprehensive and informative assessment of the existing research on LB without combining data from diverse protocols that would lead to inaccurate and misleading conclusions.

Finally, the primary outcome assessed in the Hussain analysis is area under the curve of pain scores, but that is not an appropriate outcome since most studies did not assess pain in a way to determine a trend over time. In addition, studies did not account for other analgesics to truly determine the effect of LB; healthcare professionals cannot simply leave their patients in pain when additional treatment is needed, so they are provided additional pain treatment. Evaluating mean pain scores alone tends to minimize the difference between LB and the comparator. Instead, studies that account for the fact that patients receive additional analgesics beyond the test drugs (patients cannot be left in pain; they are provided additional medication as needed), such as the PILLAR trial and the bunion repair trial discussed above, assess more informative outcomes.

For these reasons, the analysis the Hussain review authors conducted does not support a conclusion that LB is not superior to non-liposomal anesthetics. Such a conclusion is false and misleading.

B. The Conclusions of the Ilfeld Review Are Likewise False.

The article by Ilfeld et al. falsely proclaims that "the preponderance of current evidence fails to support the routine use of liposomal bupivacaine over standard local anesthetics when treating postoperative pain."[55] It then magnifies the import a reader would give to that conclusion by claiming that the authors reached the conclusion after conducting "*a comprehensive summary* of all randomized, controlled trials (n = 76) involving the clinical use of liposomal bupivacaine when administered to control acute postsurgical pain."[56] The article's summary of these trials is not comprehensive; instead, it presents little more than the authors' subjective characterizations of the studies under review—presented as though they were fact—without any systematic method to identify, evaluate, or analyze their results (i.e., using a specific methodology to address pre-specified questions). The authors' inaccurate statements and characterizations have the cumulative effect of distorting the truth of the evidence with respect to LB.

As an initial matter, the Ilfeld article suffers from the same principal flaw as the Hussain article, applying inappropriate comparisons of divergent studies to support the article's conclusions. Despite acknowledging that the articles under review "are not easily compared," the authors nonetheless make such comparisons, such as grouping and evaluating trials involving vastly different surgical procedures—obscuring the important fact that LB's efficacy varies by specific surgical area and technique used.

[55] Ilfeld at 333.
[56] Ilfeld at 283 (emphasis added).

With the exception of knee-replacement studies, the authors group all other studies only by the anesthesia procedure (e.g., direct infiltration of LB versus a placebo,[57] or direct infiltration of LB versus a non-liposomal peripheral nerve block[58]), rather than by surgical procedure, anesthesia procedure, analgesic regimen, and testing protocols. For example, the authors rely on 16 different trials involving a peripheral nerve block or epidural with LB, though these studies evaluated heterogeneous surgical procedures, experimental treatments, and comparison groups, including anatomic locations beyond those for which LB is FDA-approved.[59] The authors also group together 19 studies involving vastly different surgical procedures—including oral dental implant surgery, hemorrhoidectomy, breast augmentation, inguinal hernia repair, orthopedic wrist surgery, and total hip arthroplasty, among others. Many of these 19 studies involve procedures for which the optimal dose and technique for LB has not yet been identified. In the absence of any methodological consistency, the authors still use these results to conclude that there is no difference in effectiveness of LB versus a local anesthetic for "procedures other than knee arthroplasty."[60] Much like the Hussain article, these studies should not have been reviewed together in the first place, but having done so, the only reasonable conclusion that could be drawn from these varied procedures is that there was insufficient evidence from which to draw an accurate conclusion. By synthesizing these highly diverse trials and drawing a conclusion from that exercise, the authors reach false and misleading conclusions.

Additionally, the studies that are unfavorable to LB on which the Ilfeld et al. authors rely are categorically inferior. The authors are quick to dismiss industry-sponsored studies.[61] Not only is that wrong from a methodological perspective, it also excludes superior tests. Here, as a general matter, the industry-sponsored studies were much better funded than the independent studies, which is important in two key respects. First, the studies were able to undertake the labor-intensive and challenging process of collecting data that would allow the researchers to account for the additional analgesics (the rescue medication) that the trial patients received. This is an important undertaking. Without doing so, a reduced pain score would be incorrectly attributed to the study drug and not to opioids or other pain medication provided the patient, thereby introducing bias into the findings. Indeed, the European Medicines Agency (EMA),[62] as well as the National Research Council (at the request of the FDA),[63] provide recommendations on imputation methods to minimize bias. Modern methods, such as multiple imputation, which were used in more recent industry-sponsored LB trials, are preferred. The underlying independent studies that Ilfeld assesses *do not make any effort to impute the missing data.*

Second, the industry-sponsored studies had sufficient resources to control for attrition; i.e., study patients were not released from the hospital before data could be collected for the primary outcome. Independent studies typically lack the funding to require all patients to remain

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[57] Ilfeld at 285.
[58] Ilfeld at 310.
[59] Ilfeld at 319.
[60] Ilfeld at 290-301.
[61] Ilfeld at 332-33.
[62] EMA, Guideline on Missing Data in Confirmatory Clinical Trials, at 9, available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-missing-data-confirmatory-clinical-trials_en.pdf.
[63] Prevention and Treatment of Missing Data in Clinical Trials at 2, available at https://www.cytel.com/hs-fs/hub/1670/file-2411099288-pdf/Pdf/MissingDataNationalAcademyofMedicine.2010.pdf.

in the hospital for the primary study period, especially because early discharge has become a priority. Therefore, fewer patients remain in the hospital at the later time points, and those who require a longer hospital stay likely have different pain or post-surgical recovery conditions than those who were able to be discharged earlier. This will likely introduce bias in assessments of later time points. One example can be found in the total knee arthroplasty study conducted by Suarez et al.[64] One outcome the study looked at was pain and opioid use at 48 hours after surgery, however 10% of patients were discharged before that time, and no effort was made to impute missing data or collect data from patients after discharge. Nevertheless, Ilfeld et al. only cited "some concerns" in their assessment of the risk of study bias.[65]

In addition, in many respects, the authors discredit studies that support the increased effectiveness of LB, leading the authors to ignore, dismiss, or obscure evidence or context that would refute the article's false conclusion, while placing undue weight on articles that are critical of LB.

First, the authors seek to discredit the results of the placebo-controlled trials that met the qualifications for FDA approval. They criticize those trials for using the "windowed worst observation carried forward + last observation carried forward" imputation method for accounting for the additional analgesics patients received. As an initial matter, this criticism is absurd because the independent, unfavorable LB studies made *no effort at all* to impute for the rescue medication.

Further, the authors quote, as the basis of their criticism, a perspective published in 2012 that states, "Single imputation methods like last observation carried forward and baseline observation carried forward should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified."[66] But this reference does not apply. It is referring to single imputation methods, which *were not used in any of the LB placebo-controlled registration studies*, and it *does not discuss windowed worst observation carried forward*. Instead, the placebo trials combined both last observation carried forward and worst observation carried forward (a combined, rather than a single imputation method) with additional imputations used to conduct sensitivity analyses. This is the a more robust imputation approach than what the authors point out and was accepted by the FDA at the

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[64] Suarez JC, Al-Mansoori AA, Kanwar S, Villa JM, McNamara CA, Patel PD. Effectiveness of Novel Adjuncts in Pain Management Following Total Knee Arthroplasty: A Randomized Clinical Trial. J Arthroplasty. 2018.

[65] The authors are particularly (and wrongly) dismissive of the PILLAR study. The authors criticize the study for not reporting out all of the pain data, implying that the study was hiding an outcome [Ilfeld at 310]. But the data simply was not reported in the publication nor was it requested during the peer review, as it was not pertinent to the primary outcomes (which looked to pain in the context of opioid consumption). The PILLAR study reached the remarkable conclusion that when LB was compared to an already effective pain multi-modal pain regimen, it still reduced opioid consumption **78%** over the established regimen. The Ilfeld authors next claim that the PILLAR study deviated from the prespecified statistical plan, citing a letter to the editor [*id.*], but the authors omit that the issue was addressed in a published response to that letter. As noted in the response, appropriate tests were applied in the final analysis, and as is often the case in clinical trials, the statistical plan was altered during the course of the study, *before* data was unblinded. [Mont MA, et al. Response to Letter to the Editor on "Local Infiltration Analgesia With Liposomal Bupivacaine Improves Pain Scores and Reduces Opioid Use After Total Knee Arthroplasty: Results of a Randomized Controlled Trial." J Arthroplasty. 2018; 33(8):2694-5.]

[66] Ilfeld at 285 (*quoting* O'Neill RT, Temple R: The prevention and treatment of missing data in clinical trials: An FDA perspective on the importance of dealing with it. Clin Pharmacol Ther 2012; 91:550–4).

time.[67] Imputations are performed ensure that the predictions are reliable and are standard practice when reporting findings to the FDA. Indeed, lead author Brian Ilfeld himself used this combined method for an RCT he co-authored that compared LB to a placebo in femoral nerve blocks for total knee arthroplasty (knee replacements). Ilfeld's RCT reported both the imputed and non-imputed "area under the curve" pain scores to confirm that findings remained highly significant in favor of LB (P=0.0005).[68]

Second, the authors discuss "risk of bias" assessments using the Cochrane bias tool, which they state leads to a conclusion that "there is currently no published evidence with a low risk of bias for surgical procedures other than knee arthroplasty demonstrating that infiltration with the maximum approved liposomal bupivacaine dose is superior to unencapsulated bupivacaine to a statistically and clinically significant degree."[69] Notably, the Cochrane bias tool explicitly excludes industry funding as a measure of potential bias, in part because industry-funded trials often produce some of the better designed studies. Accordingly, the source of study funding should have been irrelevant to the authors' evaluations of the studies. Despite this exclusion, the authors impute their own measure of bias to undermine the validity of studies otherwise supportive of the effectiveness of LB, stating that LB was most often found superior in studies "with a conflict —including funding from the manufacturer, as well as funding of authors concurrently being paid as consultants and/or employees."[70]

Third, the authors contend that a high risk of bias was present in a study supporting LB whenever there was a difference between the primary outcome provided in the clinicaltrials.gov registry entry versus the outcome identified in the published manuscript. The authors do not address published explanations for the cause of such differences,[71] presenting a one-sided view that fails to meet the "comprehensive" summary claimed by the authors. Yet even when Ilfeld et al. chose to disregard the primary outcomes of the studies supporting the effectiveness of LB due to "risk of bias," the authors had no issue setting these concerns aside to conclude that the secondary outcomes of the same set of studies demonstrated that local anesthetics are superior to LB.[72]

Fourth, the Ilfeld authors assert that LB-favorable studies provided sub-maximal doses of bupivacaine as a control. The authors must know that this is not a legitimate criticism. Regardless of the dose given, when given as a single dose, plain bupivacaine confers a benefit only in the early postoperative period, while LB provides analgesia for an extended period after surgery. The short duration of bupivacaine is generally bridged by other medications to provide pain relief further out from the surgery. Thus, the authors are comparing apples to oranges when looking at the pain medication dosage intended for immediate postoperative relief to the dosage meant for multiple days after surgery. Additionally, there is no standard dosing established for

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[67] Ilfeld at 285.
[68] Hadzic A, Minkowitz HS, Melson TI, Berkowitz R, Uskova A, Ringold F, et al. Liposome Bupivacaine Femoral Nerve Block for Postsurgical Analgesia after Total Knee Arthroplasty. Anesthesiology. 2016;124(6):1372-83.
[69] Ilfeld at 301.
[70] Ilfeld at 333.
[71] *See, e.g.*, Mont MA, et al. Response to Letter to the Editor on "Local Infiltration Analgesia With Liposomal Bupivacaine Improves Pain Scores and Reduces Opioid Use After Total Knee Arthroplasty: Results of a Randomized Controlled Trial." J Arthroplasty. 2018; 33(8):2694-5.
[72] *See, e.g.*, Ilfeld at 310-11 ("Secondary outcomes allow a comparison of liposomal bupivacaine infiltration and peripheral nerve blocks.").

bupivacaine for many surgical procedures. For example, in trials related to a total knee arthroplasty ("TKA") (total knee replacement) (like the PILLAR study), the following varied doses and other mixtures were used: 266 mg LB plus epinephrine to 50 mg bupivacaine plus epinephrine;[73] 266 mg LB plus 75 mg bupivacaine to 150 mg bupivacaine alone;[74] 266 mg LB alone to 75 mg bupivacaine plus epinephrine and morphine;[75] 266 mg LB plus 75 mg bupivacaine to 75 mg bupivacaine plus lidocaine, epinephrine, morphine, and ketorolac;[76] and 266 mg LB alone to 100 mg bupivacaine.[77] In addition, the authors acknowledge that the dose of ropivacaine was adequate in the TKA study by Snyder et al., which also had a low risk of bias, and positive findings in favor of LB,[78] thereby contradicting their own assessment.

Fifth, while the authors provide extended discussion of the quality of studies supporting LB, they fail to do the same for the studies that do not support LB. Instead, the authors give more weight to studies with findings against LB and remain silent about their flaws. For example, they describe the Danoff et al. TKA study, which used patients as their own controls by using LB for a knee replacement on one knee and bupivacaine for a replacement of the second knee, as "a unique and illuminating investigation" with an "especially powerful" design (p. 301).[79] But the Ilfeld authors fail to acknowledge major methodologic flaws, including lack of allocation concealment, lack of blinding of the surgeon, lack of data on the percent of patient data available at each time point, and selective reporting, all of which can introduce significant bias.[80]

In addition, the Ilfeld authors identified the following TKA studies as a low risk of bias or as only having "some concerns," when, in fact, many have large flaws that can introduce significant bias:

[73] Alijanipour P, Tan TL, Matthews CN, et al. Periarticular Injection of Liposomal Bupivacaine Offers No Benefit Over Standard Bupivacaine in Total Knee Arthroplasty: A Prospective, Randomized, Controlled Trial. The Journal of Arthroplasty. 2017;32(2):628-634.
[74] Schroer WC, Diesfeld PG, LeMarr AR, Morton DJ, Reedy ME. Does Extended-Release Liposomal Bupivacaine Better Control Pain Than Bupivacaine After TKA? A Prospective, Randomized Clinical Trial. *J Arthroplasty.* 2015;30(9):64-67.
[75] Jain RK, Porat MD, Klingenstein GG, Reid JJ, Post RE, Schoifet SD. Liposomal Bupivacaine and Periarticular Injection Are Not Superior to Single-Shot Intra-articular Injection for Pain Control in Total Knee Arthroplasty. *J Arthroplasty.* 2016;31(9):22-25.
[76] Suarez JC, Al-Mansoori AA, Kanwar S, Villa JM, McNamara CA, Patel PD. Effectiveness of Novel Adjuncts in Pain Management Following Total Knee Arthroplasty: A Randomized Clinical Trial. *J Arthroplasty.* 2018.
[77] Zlotnicki JP, Hamlin BR, Plakseychuk AY, Levison TJ, Rothenberger SD, Urish KL. Liposomal Bupivacaine vs Plain Bupivacaine in Periarticular Injection for Control of Pain and Early Motion in Total Knee Arthroplasty: A Randomized, Prospective Study. J Arthroplasty. 2018;33(8):2460-2464.
[78] Snyder MA, Scheuerman CM, Gregg JL, Ruhnke CJ, Eten K. Improving total knee arthroplasty perioperative pain management using a periarticular injection with bupivacaine liposomal suspension. *Arthroplasty Today.* 2016; 2(1):37-42.
[79] Ilfeld at 301.
[80] Danoff JR, Goel R, Henderson RA, Fraser J, Sharkey PF. Periarticular Ropivacaine Cocktail Is Equivalent to Liposomal Bupivacaine Cocktail in Bilateral Total Knee Arthroplasty. *J Arthroplasty.* 2018; 33(8):2455-2459.

Table 4. Bias Risk Assessment of TKA Studies

Author, Year, Procedure, N	Ilfeld Risk of Bias Assessment	Risk of Bias Assessment (⊕ not flawed; ⊖ possibly flawed; ⊖ flawed)
Schroer 2015 Unilateral TKA N=111[81]	Some concerns	⊖ Randomization ⊖ Allocation concealment ⊕ Blinding ⊖ Attrition bias? Study period not defined, no data on % available at each time point ⊖ Selective reporting: opioid units not reported
Collins 2016 Primary unilateral TKA N=105[82]	Some concerns	⊖ Randomization not described ⊖ Allocation concealment ⊖ Blinding (nurses randomizing and assessing) ⊖ Attrition bias? Study period not defined, no data on % available at each time point ⊖ Selective reporting: not all outcomes reported
Jain 2016 Unilateral TKA N=207[83]	Low	⊕ Randomization ⊖ Allocation concealment ⊖ Blinding (surgeons collected data) ⊖ Attrition bias? Study period not defined, no data on % available at each time point, but mean is <2 d ⊖ Selective reporting: pain assessment methods not described, all data collected from medical records
Schwarzkopf 2016 Primary unilateral TKA N=38[84]	Low	⊖ Randomization not described ⊖ Allocation concealment not described, surgeon not blinded ⊕ Blinding ⊖ Selective reporting: not all data reported, pain assessment methods not described – all data collected via clinical assessment records ⊖ Attrition bias? Study period not defined; no data on % available at each time point
Barrington 2017 Primary unilateral TKA N=119[85]	Low	⊕ Randomization ⊖ Allocation concealment ⊖ Blinding of participants/personnel – study coordinator not blinded ⊕ Attrition bias ⊕ Selective reporting
DeClaire 2017 Unilateral TKA N=96[86]	Low	⊕ Randomization ⊕ Allocation concealment ⊕ Blinding ⊖ Pain assessment methodology not described and incomplete reporting of outcomes (Selective reporting bias) ⊖ Attrition bias?: % followed through 48 hrs not reported ⊖ Potential underpowering of results (incomplete recruitment)

[81] Schroer WC, Diesfeld PG, LeMarr AR, Morton DJ, Reedy ME. Does Extended-Release Liposomal Bupivacaine Better Control Pain Than Bupivacaine After TKA? A Prospective, Randomized Clinical Trial. *J Arthroplasty*. 2015; 30(9):64-67

[82] Collis PN, Hunter AM, Vaughn MDD, Carreon LY, Huang J, Malkani AL. Periarticular Injection After Total Knee Arthroplasty Using Liposomal Bupivacaine vs a Modified Ranawat Suspension: A Prospective, Randomized Study. *The Journal of Arthroplasty*. 2016; 31(3):633-636.

[83] Jain RK, Porat MD, Klingenstein GG, Reid JJ, Post RE, Schoifet SD. Liposomal Bupivacaine and Periarticular Injection Are Not Superior to Single-Shot Intra-articular Injection for Pain Control in Total Knee Arthroplasty. *J Arthroplasty*. 2016; 31(9):22-25.

[84] Schwarzkopf R, Drexler M, Ma MW, et al. Is There a Benefit for Liposomal Bupivacaine Compared to a Traditional Periarticular Injection in Total Knee Arthroplasty Patients With a History of Chronic Opioid Use? *Journal of Arthroplasty*. 2016; 31(8):1702-1705.

[85] Barrington JW, Emerson RH, Lovald ST, Lombardi AV, Berend KR. No Difference in Early Analgesia Between Liposomal Bupivacaine Injection and Intrathecal Morphine After TKA. *Clin Orthop Relat Res.* 2017; 475(1):94-105.

[86] DeClaire JH, Aiello PM, Warritay O, Freeman DC. Effectiveness of Bupivacaine Liposome Injectable Suspension for Postoperative Pain Control in Total Knee Arthroplasty: A Prospective, Randomized, Double Blind, Controlled study. *The Journal of Arthroplasty.* 2017;3 2(9):S268-S271.

Author, Year, Procedure, N	Ilfeld Risk of Bias Assessment	Risk of Bias Assessment (⊕ not flawed; ⊖ possibly flawed; Θ flawed)
Danoff 2018 Bilateral TKA and unicompart-mental knee arthroplasty N=52[87]	Some concerns	⊕ Randomization Θ Allocation concealment –per surgeon's protocol Θ Blinding – data captured by clinical chart review, surgeon not blinded ⊖ Attrition bias? no data on % available at each time point Θ Selective reporting: not all data reported, all data collected via clinical assessment records
Suarez 2018 Unilateral TKA N=156[88]	Some concerns	⊕ Randomization ⊖ Allocation concealment – not described Θ Blinding - single blinded Θ Attrition bias – 10% discharged before end of primary study period ⊕ Selective reporting
Zlotnicki 2018 Primary unilateral TKA N=80[89]	Some concerns	⊖ Randomization method not described ⊖ Blinding method not described Θ Allocation concealment – drug prepared in OR ⊖ Attrition bias? no data on % available at each time point Θ Selective reporting: differences in baseline characteristics, not all data reported, all data collected via clinical assessment records, pain assessments not described; no power analysis was performed
Schumer 2019 Primary unilateral TKA N=195[90]	Low	⊖ Randomization method not described ⊖ Allocation concealment – not described Θ Blinding - single blinded, blinding method not described ⊖ Attrition bias? no data on % available at each time point Θ Selective reporting: not all data reported, all data collected via clinical assessment records, pain assessments not described; no power analysis was performed
Hyland 2019 Unilateral TKA N=59[91]	Low	⊖ Randomization method not described Θ Allocation concealment – revealed after consent Θ Blinding – single blinded, blinding method not described ⊕ Attrition bias Θ Selective reporting: all data collected via clinical records, no information on for assessment standards

In fact, the TKA studies with the lowest risk of bias, (i.e., the highest quality studies) are favorable to LB.

Finally, the authors fail to specifically call out studies that compare LB single administration to a continuous infiltration of short-acting local anesthetic. Continuous infiltration of a plain local anesthetic is a more appropriate comparator to LB as it can provide analgesia for a similar duration as LB. Five RCTs are described below that show comparable to superior findings of LB compared to continuous infiltration of plain local anesthetics.

[87] Danoff JR, Goel R, Henderson RA, Fraser J, Sharkey PF. Periarticular Ropivacaine Cocktail Is Equivalent to Liposomal Bupivacaine Cocktail in Bilateral Total Knee Arthroplasty. *J Arthroplasty*. 2018; 33(8):2455-2459.
[88] Suarez JC, Al-Mansoori AA, Kanwar S, Villa JM, McNamara CA, Patel PD. Effectiveness of Novel Adjuncts in Pain Management Following Total Knee Arthroplasty: A Randomized Clinical Trial. *J Arthroplasty*. 2018.
[89] Zlotnicki JP, Hamlin BR, Plakseychuk AY, Levison TJ, Rothenberger SD, Urish KL. Liposomal Bupivacaine vs Plain Bupivacaine in Periarticular Injection for Control of Pain and Early Motion in Total Knee Arthroplasty: A Randomized, Prospective Study. *J Arthroplasty*. 2018; 33(8):2460-2464.
[90] Schumer G, Mann JW, 3rd, Stover MD, Sloboda JF, Cdebaca CS, Woods GM. Liposomal Bupivacaine Utilization in Total Knee Replacement Does Not Decrease Length of Hospital Stay. *J Knee Surg*. 2019;32(9):934-939.
[91] Hyland SJ, Deliberato DG, Fada RA, Romanelli MJ, Collins CL, Wasielewski RC. Liposomal Bupivacaine Versus Standard Periarticular Injection in Total Knee Arthroplasty With Regional Anesthesia: A Prospective Randomized Controlled Trial. *J Arthroplasty*. 2019; 34(3):488-494.

Table 5. Excluded LB Single-Administration vs. Continuous Infiltration of Local Anesthetic

Procedure	Study Design	Results
Open Laparotomy	**Yalamanchili et al 2019**[92] *Double-blinded RCT* Local infiltration LB + PCA vs continuous bupivacaine infiltration + PCA vs. PCA alone (N=100)	• 52% less opioid consumption vs PCA alone through postoperative day (POD) 3 (101 vs. 210 MME, P<0.001) • 43% less opioid consumption than continuous bupivacaine + PCA through POD3 (101 vs. 178 MME, P<0.001) • Significantly less pain reported on POD1 and POD3 vs both groups (P<0.005) • Significantly lower incidence of nausea and vomiting (10% vs. 24% continuous bupivacaine, and vs. 39% PCA only, P=0.001) • Comparable hospital stay
Abdominal oncologic surgery	**Shaker et al 2018**[93] *Open-label RCT* LB TAP vs. epidural (N=67)	• 69% less opioid consumption overall with comparable pain control through POD 3 o POD0: 36.3 vs 112.8 MME, P<0.001 o POD1: 33 vs 120.2 MME, P<0.001 o POD2: 24.5 vs 84.2 MME, P=0.001 o POD3: 21.3 vs 60 MME , P=0.001 • Fewer episodes of hypotension through POD1 (0.6 vs 3, P=0.02)
Colorectal Procedures	**Torgeson et al 2018**[94] *Nonblinded RCT* LB TAP vs. epidural (N=83)	• Shorter hospital stay (3.3 vs 2.8 days P=0.023) • Comparable time to flatus • Comparable nausea and vomiting
Colorectal Procedures	**Felling et al 2018**[95] *Open-label RCT* LB TAP vs. epidural (N=179)	• 52% less opioid consumption (98.29 vs 206.84 MME, P<0.001) o POD0: 54.64 vs. 80.28 MME, P=0.02 o POD1: 13.34 vs. 71.0 MME, P<0.001 o POD2: 2.61 vs. 3.11 MME, P=0.726 o POD3: 0.22 vs. 0.34 MME , P=0.1418 • Similar reported pain, time to GI function, hospital stay, and postoperative complications • $357 cost savings per patient

[92] Yalamanchili H, Thorns J, Buchanan S, McKenzie N, Reiss A, Price P, et al. Post laparotomy pain management: Patient controlled analgesia pump alone versus adjunctive continuous subcutaneous bupivacaine infusion or injection of liposomal bupivacaine suspension. Journal of Opioid Management. 2019; 15(2): 169-175.

[93] Shaker TM, Carroll JT, Chung MH, Koehler TJ, Lane BR, Wolf AM, et al. Efficacy and safety of transversus abdominis plane blocks versus thoracic epidural anesthesia in patients undergoing major abdominal oncologic resections: A prospective, randomized controlled trial. American Journal of Surgery. 2018;215(3):498-501.

[94] Torgeson M, Kileny J, Pfeifer C, Narkiewicz L, Obi S. Conventional Epidural vs Transversus Abdominis Plane Block with Liposomal Bupivacaine: A Randomized Trial in Colorectal Surgery. J Am Coll Surg. 2018; 227(1):78-83.

[95] Felling DR, Jackson MW, Ferraro J, Battaglia MA, Albright JJ, Wu J, et al. Liposomal Bupivacaine Transversus Abdominis Plane Block Versus Epidural Analgesia in a Colon and Rectal Surgery Enhanced Recovery Pathway: A Randomized Clinical Trial. Dis Colon Rectum. 2018; 61(10):1196-204.

Abdominal based unilateral breast reconstruction	**Gatherwright et al 2018**[96] *Blinded RCT* LB TAP vs. Bupivacaine TAP vs. Continuous bupivacaine TAP vs. Historical control (N=27)	• 49% less total opioid use vs. single administration bupivacaine TAP through 72 hrs (40.9 vs 79.9 MME, P=0.002) • 23% less total opioid use vs. continuous bupivacaine TAP through 72 hrs (40.9 vs 53.2 MME, P<0.001) • 58% less total opioid use vs. controls through 72 hrs (40.9 vs 97.6 MME, P=0.006) • Similar pain scores across groups • Similar hospital stay across all groups (3.7 days)

This table shows that LB is effective compared to continuous infiltration of bupivacaine, especially with respect to reduced opioid consumption.

For these reasons, the authors of the Ilfeld narrative review represents the authors' biased, slanted, and misleading views about LB, masquerading as scientific facts.

C. The Conclusions of the McCann Editorial Are False.

In addition to the above articles, the editors of *Anesthesiology* invited publication of a guest editorial addressing the same subject as the Hussain and Ilfeld articles. The editorial, written by Dr. Mary Ellen McCann, reiterates and adopts the deeply flawed methodology and false conclusions of the Hussain and Ilfeld articles, while utilizing a similarly biased presentation of the evidence. Rather than provide an independent and unbiased review of the evidence, the McCann article is structured to support a false narrative that impugns the actions and motives of Pacira Biosciences and thousands of physicians who have used LB in patient care: that despite published studies supporting LB's effectiveness, the only reason this new, non-opioid treatment for pain is used by clinicians is the manufacturer's research, education, and consulting arrangements with physicians.

The McCann article first undermines, without justification, the results of studies in which LB was found to be superior to bupivacaine. For instance, despite acknowledging that the Cochrane Risk of Bias tool used by both Ilfeld and Hussain does not measure conflicts of interest by industry funding, McCann immediately implies that such funding creates bias, noting that LB was superior to comparators in 46% of trials with direct funding or financial support for the authors by the manufacturer of LB but was found superior in only 11% of the "nonconflicted" trials. No other explanation or evaluation of these different studies is provided; only a statement that this fact is "not surprising."

To continue the narrative, McCann selectively identifies additional subgroups of studies or analyses that support the effectiveness or superiority of LB, and then consistently dismisses the results by implying they are tainted by conflict or bias—even when no such bias was identified in the underlying analysis. For example, in the discussion of the Ilfeld review, the McCann article notes that of a group of 28 trials, 43% (n=12) showed superiority of LB. Rather

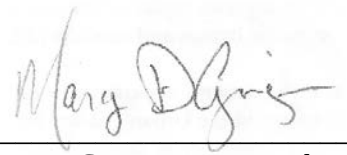
[96] Gatherwright J, Knackstedt R, Ghaznavi A, Bernard S, Schwarz G, Moreira A, et al. Prospective, Randomized, Controlled Comparison of Local Anesthetic Infusion Pump versus DepoFoam Bupivacaine For Pain Management After Unilateral Delayed Deep Inferior Epigastric Perforator Free Flap Reconstruction. Plast Reconstr Surg. 2018.

than discuss these study results or the procedures, McCann's next statement is that 82% of the 28 trials (n=23) showed "high risk or some concerns for bias." McCann does not discuss whether any of the 12 studies showing superiority of LB were outside the group of 23 studies showing a high risk or some concern or bias. The article ignores the Cochrane standards for methodologic bias. She instead leaves the reader only with the implication that studies favorable to LB were biased, and the false conclusion of the Ilfeld article that "the preponderance of current evidence fails to support the routine use of liposomal bupivacaine over standard local anesthetics when treating postoperative pain."[97]

Also note that the McCann and Ilfeld articles suggest LB has an unusually high number of Pacira-funded studies,[98] when in fact this is typical of a non-generic product, as the cost to conduct a quality study is high and not likely to be funded by other entities. The Cochrane handbook notes: "Industry funding is common, especially in drug trials. In a study of 200 trial publications from 2015, 68 (38%) of 178 trials with funding declarations were industry funded (Hakoum et al 2017[99]). Also, in a cohort of oncology drug trials, industry funded 44% of trials and authors declared conflicts of interest in 69% of trials (Riechelmann et al. 2007[100])."[101]

Each of the separate mischaracterizations and falsehoods serves to undermine or dismiss the accumulated evidence demonstrating the effectiveness of LB and its superiority over non-liposomal bupivacaine documented in multiple studies. These mischaracterizations culminate in the final unsupported and false allegation by Dr. McCann: that the use of LB by hospitals and licensed physicians over the prior eight years is due in sole or large part to an "aggressive and powerful marketing strategy" by Pacira Biosciences. In fact, the use of LB goes far beyond Pacira's marketing efforts into novel areas, as demonstrated by the broad range of procedural areas for which it is used. The implied causal relationship between the manufacturer's total expenditures on research and other services provided by physicians from 2013 to 2019, and the increased sales of LB during this time, defames the character of the manufacturer and the motives of all of the healthcare providers that chose to use LB in the treatment of their patients. This final and most egregious implication by McCann is unsupported by any evidence linking the appropriate public disclosures made by the manufacturer and the independent clinical decisions of these healthcare providers to use LB.

April 14, 2021



Mary DiGiorgi, M.P.H., Ph.D

[97] McCann M. Liposomal Bupivacaine: Effective, Cost-effective, or (Just) Costly?. Anesthesiology. 2021; 134(2):139-142, at 140 ("McCann Editorial").
[98] McCann Editorial at 139; Ilfeld Review at 333.
[99] Hakoum MB, Jouni N, Abou-Jaoude EA, Hasbani DJ, Abou-Jaoude EA, Lopes LC, Khaldieh M, Hammoud MZ, Al-Gibbawi M, Anouti S, Guyatt G, Akl EA. Characteristics of funding of clinical trials: cross-sectional survey and proposed guidance. BMJ Open 2017; 7: e015997.
[100] Riechelmann RP, Wang L, O'Carroll A, Krzyzanowska MK. Disclosure of conflicts of interest by authors of clinical trials and editorials in oncology. Journal of Clinical Oncology 2007; 25: 4642-4647.
[101] 7.8.1 Characteristics of conflicts of interest#section-7-8-1, available at https://training.cochrane.org/handbook/current/chapter-07.

APPENDIX I

Methods for selecting head-to-head studies:
An automated search of the MEDLINE/PubMed database, and EMBASE database has been established to retrieve all EXPAREL studies utilizing the following search terms: "bupivacaine AND depofoam OR (bupivacaine AND liposom*) OR (bupivacaine AND multivesicul*) OR (bupivacaine AND extend* AND release) OR (bupivacaine AND pacira) OR depobupivacaine OR exparel OR 'bupivacaine liposome injectable suspension'". Those meeting the criteria outlined below are included in the evidence summary.

Selection Criteria

Studies included:
- Randomized controlled trials (RCTs) or observational studies (Obs) comparing LB to single or continuous administration (via catheter) of an immediate release local anesthetic (eg bupivacaine, ropivacaine, lidocaine) for local/regional analgesia
- Studies reporting at least one of the following outcomes: postoperative pain, opioid consumption, hospital stay/discharge, function
- Studies published in a peer reviewed journal between January 1, 2011 through February 28, 2021

Excluded:
- Studies which compared LB to placebo or non-regional anesthesia modalities (eg systemic oral or IV analgesics alone)
- Studies which evaluated LB in combination with other interventions (eg an enhanced recovery protocol vs traditional recovery protocol)
- Studies in animals
- Studies in healthy volunteers
- Case reports or series
- Abstracts or posters

APPENDIX II

Citations for head-to-head studies

Colorectal

Haas E, Onel E, Miller H, Ragupathi M, White PF. A double-blind, randomized, active-controlled study for post-hemorrhoidectomy pain management with liposome bupivacaine, a novel local analgesic formulation. Am Surg. 2012; 78(5):574-81.

Knudson RA, Dunlavy PW, Franko J, Raman SR, Kraemer SR. Effectiveness of Liposomal Bupivacaine in Colorectal Surgery: A Pragmatic Nonsponsored Prospective Randomized Double Blinded Trial in a Community Hospital. Diseases of the colon and rectum. 2016; 59(9):862-9.

Stokes AL, Adhikary SD, Quintili A, Puleo FJ, Choi CS, Hollenbeak CS, et al. Liposomal Bupivacaine Use in Transversus Abdominis Plane Blocks Reduces Pain and Postoperative Intravenous Opioid Requirement After Colorectal Surgery. Diseases of the colon and rectum. 2017; 60(2):170-7.

Felling DR, Jackson MW, Ferraro J, Battaglia MA, Albright JJ, Wu J, et al. Liposomal Bupivacaine Transversus Abdominis Plane Block Versus Epidural Analgesia in a Colon and Rectal Surgery Enhanced Recovery Pathway: A Randomized Clinical Trial. Diseases of the colon and rectum. 2018; 61(10):1196-204.

Torgeson M, Kileny J, Pfeifer C, Narkiewicz L, Obi S. Conventional Epidural vs Transversus Abdominis Plane Block with Liposomal Bupivacaine: A Randomized Trial in Colorectal Surgery. J Am Coll Surg. 2018; 227(1):78-83.

Guerra L, Philip S, Lax EA, Smithson L, Pearlman R, Damadi A. Transversus Abdominis Plane Blocks in Laparoscopic Colorectal Surgery: Better Pain Control and Patient Outcomes with Liposomal Bupivacaine than Bupivacaine. The American Surgeon. 2019; 85(9):1013-6.

Fields AC, Weiner SG, Maldonado LJ, Cavallaro PM, Melnitchouk N, Goldberg J, et al. Implementation of liposomal bupivacaine transversus abdominis plane blocks into the colorectal enhanced recovery after surgery protocol: a natural experiment. Int J Colorectal Dis. 2020; 35(1):133-8.

Cardiothoracic

Balkhy HH, Arnsdorf S, Krienbring D, Urban J. Liposome Bupivacaine for Postsurgical Analgesia in Patients Undergoing Robotically Assisted Cardiac Surgery. Innovations. 2015; 10(6):416-9.

Khalil KG, Boutrous ML, Irani AD, Miller CC, Pawelek TR, Estrera AL, et al. Operative Intercostal Nerve Blocks With Long-Acting Bupivacaine Liposome for Pain Control After Thoracotomy. Ann Thorac Surg. 2015; 100(6):2013-8.

Rice DC, Cata JP, Mena GE, Rodriguez-Restrepo A, Correa AM, Mehran RJ. Posterior Intercostal Nerve Block With Liposomal Bupivacaine: An Alternative to Thoracic Epidural Analgesia. Ann Thorac Surg. 2015; 99(6):1953-60.

Mehran RJ, Walsh GL, Zalpour A, Cata JP, Correa AM, Antonoff MB, et al. Intercostal Nerve Blocks With Liposomal Bupivacaine: Demonstration of Safety, and Potential Benefits. Seminars in thoracic and cardiovascular surgery. 2017; 29(4):531-7.

Parascandola SA, Ibanez J, Keir G, Anderson J, Plankey M, Flynn D, et al. Liposomal bupivacaine versus bupivacaine/epinephrine after video-assisted thoracoscopic wedge resection. Interact Cardiovasc Thorac Surg. 2017; 24(6):925-30.

Dominguez DA, Ely S, Bach C, Lee T, Velotta JB. Impact of intercostal nerve blocks using liposomal versus standard bupivacaine on length of stay in minimally invasive thoracic surgery patients. Journal of Thoracic Disease. 2018; 10(12):6873-9.

Kelley TM, Jr., Bailey DW, Sparks P, Rice R, Caddell E, Currier H, et al. Intercostal Nerve Blockade with Exparel(R) Results in Lower Opioid Usage during the First 24 Hours after Video-Assisted Thorascopic Surgery. Am Surg. 2018; 84(9):1433-8.

Levy G, Cordes MA, Farivar AS, Aye RW, Louie BE. Transversus Abdominis Plane Block Improves Perioperative Outcome After Esophagectomy Versus Epidural. Annals of Thoracic Surgery. 2018; 105(2):406-12.

Sztain JF, Gabriel RA, Said ET. Thoracic Epidurals are Associated With Decreased Opioid Consumption Compared to Surgical Infiltration of Liposomal Bupivacaine Following Video-Assisted Thoracoscopic Surgery for Lobectomy: A Retrospective Cohort Analysis. Journal of cardiothoracic and vascular anesthesia. 2018.

Louis SG, King C, Baral P, Veeramachaneni N. Liposomal Bupivacaine Enhances the Pain-Control Benefits of Uniportal Thoracoscopic Lobectomy. Ann Thorac Surg. 2019; 108(5):1514-8.

Medina M, Foiles SR, Francois M, Asche CV, Ren J, Mueller DK, et al. Comparison of cost and outcomes in patients receiving thoracic epidural versus liposomal bupivacaine for video-assisted thoracoscopic pulmonary resection. Am J Surg. 2019; 217(3):520-4.

Rincavage M, Hammond L, Reddy S, Sytsma C, Prater A, Brackbill M. Pain control using liposomal bupivacaine versus bupivacaine for robotic assisted thoracic surgery. International journal of clinical pharmacy. 2019; 41(1):258-63.

Dunham WC, Lombard FW, Edwards DA, Shi Y, Shotwell MS, Siegrist K, et al. Effect of Regional Analgesia Techniques on Opioid Consumption and Length of Stay After Thoracic Surgery. Seminars in cardiothoracic and vascular anesthesia. 2020:1089253220949434.

Marciniak DA, Alfirevic A, Hijazi RM, Ramos DJ, Duncan AE, Gillinov AM, et al. Intercostal Blocks with Liposomal Bupivacaine in Thoracic Surgery: A Retrospective Cohort Study. Journal of cardiothoracic and vascular anesthesia. 2020.

NeMoyer RE, Pantin E, Aisner J, Jongco R, Mellender S, Chiricolo A, et al. Paravertebral Nerve Block With Liposomal Bupivacaine for Pain Control Following Video-Assisted Thoracoscopic Surgery and Thoracotomy. Journal of Surgical Research. 2020; 246:19-25.

Patel KM, van Helmond N, Kilzi GM, Patel A, Bowen FW, Shersher DD, et al. Liposomal Bupivacaine Versus Bupivacaine for Intercostal Nerve Blocks in Thoracic Surgery: A Retrospective Analysis. Pain physician. 2020; 23(3):E251-E8.

Pedoto A, Noel J, Park BJ, Amar D. Liposomal Bupivacaine Versus Bupivacaine Hydrochloride for Intercostal Nerve Blockade in Minimally Invasive Thoracic Surgery. Journal of cardiothoracic and vascular anesthesia. 2020.

Tariq MM, Ullah I, Khan MB, Tahir D, Ilyas SM, Sheheryar H. Liposomal Bupivacaine is NOT Better than Bupivacaine in Limited Incision Thoracic Surgery. THE STETHO. 2020; 1(2):7-13.

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Plastic

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Transplant

Yeap YL, Fridell JA, Wu D, Mangus RS, Kroepfl E, Wolfe J, et al. Comparison of methods of providing analgesia after pancreas transplant: IV opioid analgesia versus transversus abdominis plane block with liposomal bupivacaine or continuous catheter infusion. Clinical transplantation. 2019; 33(6):e13581.

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Trauma

Sheets NW, Davis JW, Dirks RC, Pang AW, Kwok AM, Wolfe MM, et al. Intercostal Nerve Block with Liposomal Bupivacaine vs Epidural Analgesia for the Treatment of Traumatic Rib Fracture. J Am Coll Surg. 2020; 231(1):150-4.

Urologic

Knight RB, Walker PW, Keegan KA, Overholser SM, Baumgartner TS, Ebertowski JS, et al. A Randomized Controlled Trial for Pain Control in Laparoscopic Urologic Surgery: 0.25% Bupivacaine Versus Long-Acting Liposomal Bupivacaine. Journal of Endourology. 2015; 29(9):1019-24.

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Exhibit A

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RELEVANT PROFESSIONAL EXPERIENCE

Pacira Pharmaceuticals, Parsippany, NJ
Vice President, Medical Science February 2020 - Present

- Lead the process to establish a robust medical information, medical communications, publications and health outcome and value assessment plans alongside all other internal key cross-functional partners
- Provide scientific support to business units and Learning and Development team as subject matter expert on Pacira products and clinical context
- Provide scientific strategic input for the elaboration of the Brand Plans and ensure execution of the Medical Strategy
- Plan and oversee Health Outcomes and Value Assessment programs according to product life cycle management
- Lead the development of the publication, and medical communication strategy
- Provide scientific leadership to the commercial teams to assist in the development and execution of scientifically sound and compliant commercial activities
- Provide input into the design and execution of corporate-sponsored clinical studies and lead the external research program
- Maintain strong relationships with thought leaders to identify new medical opportunities for existing or new corporate products and to pursue new indications

Executive Director, Medical Science June 2019 – February 2020

- Provided strategic vision, leadership, and management of scientific communication and independent research activities, with a primary focus on publications and medical communication which consists of assimilating all relevant scientific information and development of creative ways of information dissemination
- Directed medical information team with a focus on providing scientifically sound and relevant information to external stakeholders, including standard medical information response documents, custom formulary support materials and materials used by Field Medical teams
- Acted as lead for the Grants Committee and provided advisement for investigators seeking research guidance
- Provided scientific expertise into product marketing strategies, and health outcomes research strategies
- Partnered with the Medical Division organization to support strategy, design and execution of Phase 4 company sponsored studies
- Contributed to the strategy and review Learning and Development training content in compliance with internal process
- Provided medical support to Drug Safety for any product alerts in the US
- Oversaw evaluation of data gaps and provide support to the processes related to Investigator Initiated Studies
- Collaborated with cross functional teams to provide intel on publications/presentations related to Pacira products, relevant therapeutic areas, and competitive space

Senior Director, Scientific Communications January 2017 - June 2019

- Lead strategy and execution of medical information, scientific publications and scientific communications for both internal and external stakeholders, including publications, medical communication, education and medical information
- Contributed to the development and review of sponsored and supported research protocols, manuscripts, and continuous quality improvement projects, alongside Clinical Operations and Health Outcomes and Value Assessment team
- Contributed to the development of the Medical Affairs and Health Outcomes and Value Assessment strategy and tactical plan to ensure quality of data and consistency in messaging

- Supported sNDA filing for nerve block indication of EXPAREL and acted as triage lead for the FDA Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee for the supplemental new drug application for EXPAREL (bupivacaine liposomal injectable suspension)
- Participated meetings alongside Pacira leaders to inform the Opioid Commission lead by Governor Christie

Associate Director, Health Outcomes and Value Assessment March 2016 – January 2017

- Developed deliverables to communicate economic and clinical value and disease burden to external stakeholders, including patients, physicians, and payers, and providing training for internal stakeholders to utilize tools developed.
- Designed and implemented outcomes studies that established the value of EXPAREL for formulary review and/or presentation at scientific meetings and/or publication in peer-reviewed journals
- Collaborated with statisticians on the analysis of outcomes data using clinical trial and administrative databases
- Acted as scientific advisor in development of research registries and a mobile app for outcomes data capture used by clinicians and patients

Columbia University, New York, NY July 2012 – July 2016

Assistant Professor of Surgery

Associate Director, Medical Nutrition Program for Health Professionals, *Institute of Human Nutrition*

- Led the development of a novel medical nutrition program for health professionals, which started as a certification program / CME activity and expanded to an executive master's degree program, with a focus on clinically applied biochemistry, growth and development, clinical nutrition, evidence-based medical nutrition management, patient centered care, and clinical research methodology.
- Planned the program curriculum, collaborated with faculty to develop courses and assessments, provided student advisement, thesis mentorship and strategic direction for recruitment efforts, and development of marketing materials.
- Developed CME courses in nutrition and oversaw accreditation process, student recruitment activities, and program budget.
- Collaborated on the development and implementation of faculty and program evaluations with input from peer faculty, program directors, and other stakeholders.
- Directed/taught courses in: Epidemiology, Readings in Human Nutrition, Behavior Counseling, Obesity, Medical Nutrition Management and Clinical Nutrition courses in the health professional as well as the masters of nutrition program.
- Collaborated with the American Board of Obesity Medicine to transform the obesity course into an intensive 5 day course which includes lectures from experts on the etiology, prevention and treatment as well as a review for the American Board of Obesity Medicine (ABOM) exam.

Clinical Research Director, Department of Surgery July 2008 – July 2014

- Provided strategic direction and oversaw all clinical research activities and clinical trials of the adult bariatric surgery section, including preparation for site qualification, site initiation, and monitoring visits and execution of sponsored clinical trials (>$1.5M budget), research budgeting and billing, review of CRFs and development of ICFs, subject recruitment, data management, and hiring and management of support staff.
- Collaborated with internal and external resources and investigators to enhance patient recruitment, trial plan optimization and execution of studies.
- Reviewed and maintained multiple levels of research documentation per regulatory and institutional requirements (NDAs, clinical investigator agreements, financial disclosure certification, IRB submissions, IDE reports for FDA submission, NGS requests, educational materials, financial reports, logs and CRFs, etc).
- Designed, planned and conducted independent research projects including development of study protocols and corresponding documentation for IRB approval and execution of study (ICFs, CRFs, etc)
- Conducted literature searches and prepared manuscripts for publication in peer reviewed journals.
- Analyzed data and prepared/presented findings for publication in professional journals and presentation at national conferences.
- Ensured congruence of data collection tools with source data and study protocols
- Oversaw design, programming, and management of clinical registry across all practice sites, including interface with multi-center bariatric database, and ensured congruence with accreditation requirements.

- Provided nutrition counselling for research subjects enrolled in clinical trials.
- Provided intensive emergency direction on a limited budget to successfully prepare the Center for Adolescent Bariatric Surgery for an FDA audit of their large, multi-departmental, five-year adjustable banding trial, which had not previously been staffed with research personnel.

EDUCATION

Columbia University, Graduate School of Arts and Sciences
Ph.D. in Nutritional Epidemiology and Behavioral Nutrition - 2012

Columbia University, Mailman School of Public Health
M.P.H in Epidemiology - 2007

Columbia University, Graduate School of Arts and Sciences
M.S. in Human Nutrition - 2007

Barnard College, Columbia University
B.A.; Major in English, Minor in Psychology, Pre-Medical Concentration – 1997

PROFESSIONAL ORGANIZATIONS AND COMMITTEES

- Certified Medical Publication Professional (CMPP) by the International Society of Medical Publication Professionals 2017- present
- New York Academy of Medicine - Fellow since 2014 (lead role in developing workshops for translating evidence-based nutrition guidelines for patient care in the Clinical Nutrition Section)
- Columbia College of Physicians and Surgeons Nutrition and Healthy Lifestyle Steering Committee, 2014 - 2016
- Board for Certification of Nutrition Specialists Examination Development Committee, 2014 - 2016
- American Society for Nutrition - Member since 2010
- The Obesity Society - Member since 2010
- American Society for Metabolic and Bariatric Surgery - Member since 2010
- New York Academy of Sciences - Member since 2010

PUBLICATIONS

1. Zitsman JL, **DiGiorgi MF**, Zhang AZ, Kopchinski JS, Sysko R, Devlin MJ, Fennoy I. Adolescent Gastric Banding: a 5-Year Longitudinal Study. *Obesity Surgery*. 2020 Mar;30(3):828-836.

2. Amin NH, **DiGiorgi M,** Favorito PJ. Letter to the Editor regarding Kolade et al: “Efficacy of liposomal bupivacaine in shoulder surgery: a systematic review and meta-analysis". *Journal of Shoulder and Elbow Surgery.* 2020 May;29(5):e211-e212.

3. **DiGiorgi M,** Carangelo M, Scranton R. Transversus Abdominis Plane Blocks with Single-Dose Liposomal Bupivacaine in Conjunction with a Nonnarcotic Pain Regimen Help Reduce Length of Stay following Abdominally Based Microsurgical Breast Reconstruction. *Plastic Reconstructive Surgery.* 2018 Jul;142(1):94e.

4. Zitsman JL, **DiGiorgi MF**, Fennoy I, Schauben Kopchinski J, Sysko R, Devlin MJ. Adolescent laparoscopic adjustable gastric banding (LAGB): prospective results in 137 patients followed for 3 years. *Surgery for Obesity and Related Diseases*.2015 Jan-Feb;11(1):101-9

5. Zitsman J, **DiGiorgi M**, Marr JR, Witt MA, Bessler M. Comparative outcomes of laparoscopic adjustable gastric banding (LAGB) in adolescents and adults. *Surgery for Obesity and Related Diseases*. 2011 Nov-Dec;7(6):720-6.

6. Choi J, **DiGiorgi M**, Milone L, Schrope B, Olivera-Rivera L, Daud A, Davis D, Bessler M. Outcomes of laparoscopic adjustable gastric banding in patients with low body mass index. *Surgery for Obesity and Related Diseases*. 2010 Jul-Aug;6(4):367-71.

7. Bessler M, Daud A, **DiGiorgi MF**, Inabnet WB, Schrope B, Olivero-Rivera L, Davis D. Adjustable gastric banding as revisional bariatric procedure after failed gastric bypass--intermediate results. *Surgery for Obesity and Related Diseases*. 2010 Jan-Feb;6(1):31-5.

8. **DiGiorgi M,** Rosen DJ, Choi J, Milone L, Schrope B, Olivero-Rivera L, Restuccia N, Urban-Skuro MC, Inabnet WB, Bessler M. Reemergence of Diabetes After Gastric Bypass in Patients with Mid to Long-Term Follow-Up. *Surgery for Obesity and Related Diseases*. 2010 May-Jun;6(3):249-53.

9. Harari A, Allendorf J, Shifrin A, **DiGiorgi M,** Inabnet WB. Negative preoperative localization leads to greater resource utilization in the era of minimally invasive parathyroidectomy. *American Journal of Surgery.* 2009 Jun;197(6):769-73.

10. Bessler M, Daud A, **DiGiorgi MF**, Schrope BA, Inabnet WB, Davis DG. Frequency distribution of weight loss percentage after gastric bypass and adjustable gastric banding. *Surgery for Obesity and Related Diseases*. 2008 Jul-Aug;4(4):486-91.

11. **DiGiorgi M**, Daud A, Inabnet W, Schrope B, Urban-Skuro M, Restuccia N, Bessler M. Markers of bone and calcium metabolism following gastric bypass and laparoscopic adjustable gastric banding. *Obesity Surgery.* 2008 Sep;18(9):1144-8.

12. Allendorf JA, Lauerman M, Bill A, **DiGiorgi M**, Goetz N, Vakiani E, Remotti H, Schrope B, Sherman W, Hall M, Fine RL, Chabot JA. Neoadjuvant Chemotherapy and Radiation for Patients with Locally Unresectable Pancreatic Adenocarcinoma: Feasibility, Efficacy, and Survival. *Journal of Gastrointestinal Surgery*. 2008 Jan;12(1):91-100.

13. Allendorf J, **DiGiorgi M**, Spanknebel K, Inabnet W, Chabot J, LoGerfo P. 1112 consecutive bilateral neck explorations for primary hyperparathyroidism. *World Journal of Surgery*. 2007 Nov;31(11):2075-80.

14. Bessler M, Daud A, Kim T, **DiGiorgi M**. Prospective randomized trial of banded versus nonbanded gastric bypass for the super obese: early results. *Surgery for Obesity and Related Diseases*. 2007 Jul-Aug;3(4):480-4.

15. Lew JI, Daud A, **DiGiorgi M**, Olivero-Rivera L, Davis DG, Bessler M. Preoperative esophageal manometry and outcome of laparoscopic adjustable silicone gastric banding. *Surgical Endoscopy*. 2006 Aug;20(8):1242-7.

16. Spanknebel K, Chabot JA, **DiGiorgi M**, Cheung K, Curty J, Allendorf J, LoGerfo P. Thyroidectomy using monitored local or conventional general anesthesia: an analysis of outpatient surgery, outcome and cost in 1,194 consecutive cases. *World Journal of Surgery*. 2006 May;30(5):813-24.

17. Kim TH, Daud A, Ude AO, **DiGiorgi M**, Olivero-Rivera L, Schrope B, Davis D, Inabnet WB, Bessler M. Early U.S. outcomes of laparoscopic gastric bypass versus laparoscopic adjustable silicone gastric banding for morbid obesity. *Surgical Endoscopy*. 2006 Feb;20(2):202-9.

18. Bessler M, Daud A, **DiGiorgi MF**, Olivero-Rivera L, Davis D. Adjustable gastric banding as a revisional bariatric procedure after failed gastric bypass. *Obesity Surgery*. 2005 Nov-Dec;15(10):1443-8.

19. Spanknebel K, Chabot, JA, **DiGiorgi M**, Cheung K, Lee S, Allendorf J, LoGerfo P. Thyroidectomy using local anesthesia: A report of 1,025 cases over 16 years. *Journal of the American College of Surgeons.* 2005; 201(3):375-385.

20. Spanknebel K, McConnell R, Ebner S, Saqi A, Fisher J, **DiGiorgi M**, Stolar C. Thyroidectomy in a pediatric population: Experience at a tertiary referral center. *Thyroid.* 2005; 15(S):182.

21. Spanknebel K, McConnell RJ, Chabot JA, **DiGiorgi M**, Inabnet WB, LoGerfo P. Thyroidectomy for Graves' disease: A 14-year experience in a single surgical practice. *Thyroid.* 2004; 14(9S):701.

22. Allendorf J, Kim L, Chabot J, **DiGiorgi M**, Spanknebel K, LoGerfo P. The impact of sestamibi scanning on the outcome of parathyroid surgery. *Journal of Clinical Endocrinology and Metabolism*. 2003 Jul;88(7):3015-8.

BOOK CHAPTER

1. M Bessler, D Davis, B Schrope, A Ude, N Restuccia, M Urban-Skuro, **M DiGiorgi**, "Surgical treatment of severe obesity: patient selection and screening, surgical options, and nutritional management," in *Textbook of Obesity: Biological, Psychological and Cultural Influences*, S Akabas, SA Lederman and BJ Moore, Eds. New York: John Wiley and Sons, Inc, 2012, pp. 320-332

ABSTRACT AND POSTER PRESENTATIONS

1. **DiGiorgi M**, Sangal M, Abecassis T, Restuccia N, Harvey E, Schrope B, Bagloo M, Bessler M. Low weight loss self-efficacy and childhood dieting may predict weight regain following bariatric surgery. *The Obesity Society*, Los Angeles, CA, November 2015

2. LeFauve S, **DiGiorgi M.** Feasibility and efficacy of obesity management in a primary care setting: Observations from real-life application. *The Obesity Society*, Los Angeles, CA, November 2015

3. **DiGiorgi M**, Sangal M, Abecassis T, Restuccia N, Harvey E, Schrope B, Bagloo M, Bessler M. Food Addiction and Long Term Weight Loss Outcomes Following Bariatric Surgery. *The Obesity Society*, Atlanta, GA, November 2013

4. **DiGiorgi M,** Bagloo M, Schrope B, Restuccia N, Harvey E, Bessler M. Factors Associated with Long Term Weight Regain after Bariatric Surgery. *American Society of Metabolic and Bariatric Surgery,* Atlanta, GA, November 2013

5. Bagloo M, **DiGiorgi M**, Schrope B, Silva M, Ude A, Roth A, Abecassis T, Sangal M, Bessler M, Zitsman J. One Year Outcomes of Sleeve Gastrectomy in Pediatric versus Adult Patients. *American Society of Metabolic and Bariatric Surgery,* Atlanta, GA, November 2013

6. Bagloo M, Schrope B, Ude A, **DiGiorgi M**, DeCesare L, Yang S, Harari A, Bessler M. Chronic Debilitating Gastrointestinal Symptoms: Outcomes of Gastric Bypass Reversal. *American Society of Metabolic and Bariatric Surgery,* Atlanta, GA, November 2013

7. Jonnalagadda SS, Gupta N, Eagon JC, Bessler M, Mull LN, **DiGiorgi M**, Davis D, Bhattacharya K, Cave DR, Kelly JJ, Perugini RA, Zivny J. Preliminary Results of a Randomized, Blinded, Sham-Controlled Trial of Transoral Gastroplasty for the Treatment of Morbid Obesity. *Gastroenterology.* 142 (5): Page S-78. May 2012

8. Zitsman J, **DiGiorgi M,** Schrope BA, Bessler M. Factors associated with band or port displacements among adolescents undergoing laparoscopic adjustable gastric banding (LAGB). International *Pediatric Endosurgery Group*, San Diego, CA, March 2012

9. **DiGiorgi M**, Mull L, Restuccia N, Bagloo M, Schrope B, Bessler M. Outcomes of Hispanic Patients With Medicaid Vs Private Insurance Following Gastric Bypass Surgery. *American Society of Bariatric Surgery*, Orlando, FL, June 2011

10. **DiGiorgi M**, Mull L, Restuccia N, Bagloo M, Schrope B, Bessler M. Factors associated with weight regain after gastric bypass. *American Society for Bariatric Surgery*, Orlando, FL, June 2011

11. Choi, JJ, **DiGiorgi M**, Taylor P,Daud A, Bessler M. Prospective randomized trial of banded versus non-banded gastric bypass for the super obese: five-year outcomes. *American Society for Bariatric Surgery*, Las Vegas, NV, June 2010

12. Zitsman J, **DiGiorgi M**, Marr JR, Witt MA, Bessler M. Comparative outcomes of laparoscopic adjustable gastric banding (LAGB) in adolescents and adults. *American Society for Bariatric Surgery*, Las Vegas, NV, June 2010

13. Bagloo M, Purohit M, **DiGiorgi M,** Ude A, Schrope B, Bessler M. Conversion to gastric bypass after failed lap band results in weight loss equal to primary gastric bypass. *American Society for Bariatric Surgery*, Las Vegas, NV, June 2010

14. **DiGiorgi M,** Rosen DJ, Choi J, Milone L, Schrope B, Olivero-Rivera L, Restuccia N, Urban-Skuro MC, Inabnet WB, Bessler M. Reemergence of Diabetes After Gastric Bypass in Patients with Mid to Long-Term Follow-Up. *American Society for Bariatric Surgery*, Grapevine, TX, June 2009

15. Choi J, **Digiorgi M**, Milone L, Schrope B, Olivera-Rivera L, Daud A, Davis D, Bessler M. Outcomes of laparoscopic adjustable gastric banding in patients with low body mass index. *American Society for Bariatric Surgery*, Grapevine, TX, June 2009

16. Schrope B, Allendorf J, DiNorcia J, Bill A, **DiGiorgi M**, Chabot J. A Single-Institution Retrospective Review of Laparoscopic and Open Distal Pancreatectomies. *Society for American Gastrointestinal Endoscopic Surgeons,* Las Vegas NV, April 2007.

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